Journal of the
Indian Medical Association

VOL. XV, No. 2 CALCUTTA NOVEMBER, 1945

DISCOVERY OF NEW DRUGS FOR SPECIFIC THERAPY*

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INTRODUCTION

It may seem inconceivable but nevertheless it is true that the last 15 years (1930-45) have seen new discoveries in the field of therapeutics, which were not possible in over 3000 years from 1500 B.C. (as disclosed in the records of Ebers Papyrus of Egypt) to 1618-1766 B.C., during which the first 3 editions of the London Pharmacopoeia appeared. Among the highlights of the recent therapeutic achievements may be mentioned the antimalarials, *e.g.,* Plasmochin and Atebrin in 1932-33, the anti-bacterials, *e.g.,* Prontosil and the members of the Sulphonamide family from 1935 to date, the immunologic remedies, *e.g.,* the new Cholera vaccine in 1944, remedies for the treatment of shock and war casualties with blood plasma and serum between 1942-44, the elaboration in a pure state from the blood proteins of the gamma-globulins for the prophylaxis and treatment of measles, etc., in 1944-45, the insecticides *e.g.,* D. D. T. and Gammexane for Malaria control etc., in 1942-44, the anti-biotics of the Penicillin group between 1942-45 and the latest discovery, reported only a month ago, of a new anti-malarial claimed to be at least 10 times stronger than quinine from the laboratories of the Imperial Chemical Industries, (London). It is peculiar to note that the war years (from 1939 to 1945), in spite of the wide-spread chaotic conditions associated therewith, have produced the maximum number of discoveries in the realm of drugs. It is also of interest to note that most of these discoveries have emanated from pre-war Germany, and later, from Switzerland, America and Great Britain, and that the time-lag between any individual discovery and its clinical application has been particularly short.

'TEAMWORK' IN DRUG RESEARCH

A question that naturally arises before any inquisitive mind is how this phenomenal progress is made possible? Why some countries, out of so many others, could assume leadership in the elaboration of new drugs and in their almost immediate therapeutic application during the last decade or so? How is it that remedies for some of the tropical diseases, e.g., Malaria, Leishmaniasis, Trypanosomiasis, Schistosomiasis, Yellow fever, etc., could emanate from countries where such diseases are almost non-existent? Why can't we in India emulate such examples and find remedies for such diseases as Leprosy, filariasis Leucoderma, Infantile hepatic cirrhosis, osteomalacia, etc., peculiar to India and adjoining tropical countries?

As is generally well recognised, the leadership in the field of new discoveries in synthetic and chemotherapeutic remedies was taken early in this century by Germany. An examination of the research organization and methods adopted by German scientists would therefore be expected to provide some clue to the queries referred to above. All records seem to indicate that from the time 'Antipyrine', the first synthetic drug to be introduced to the medical profession, was obtained at the Bayer Laboratories in 1888, the German chemists slowly but surely realized that a great future lay before synthetic organic chemistry and its application to medicine. German chemists, both in the commercial firms and in the Universities, intensified their efforts in the elaboration of new synthetics from various natural sources such as coal-tar, etc., but they were soon convinced that the help of pharmacologists, bacteriologists and clinicians is necessary in order to achieve any measure of success in this type of work. This realization made the Bayer Co., to start research laboratories within their works where a collaborative effort between the three types of scientists—chemists, pharmacologists and clinicians—could be fostered as in a 'team'. The first phenomenal success of this policy came through tht discovery of Salvarsan by Erhlich and Hata (1906-1908) and this was followed by a host of analgesics, and antipyretics (*e.g.,* phenacetin, pyramidon,), hypnotics (*e.g.,* veronal, luminal) anaesthetics (*e.g.,* novocain, pantocain), and chemotherapeutic remedies for protozoal and bacterial infections (*e.g.,* prontosil, uleron, atebrin). Never before in history such a glorious chapter of new discoveries of drugs could be found as was recorded in Germany within the first 35-40 years of this century.

GREAT BRITAIN AND AMERICA FOLLOW GERMAN EXAMPLE

Scientific research was already well developed in the United Kingdom and in the United States of America and it did not take them long to see the benefit of 'collaborative research', as distinguished from 'individualistic' methods which were previously in vogue in these countries. The discovery of Sulphapyridine, Gammexane and the wonder drug, Penicillin, are all examples of fruits derived from 'conjoint efforts' of various groups of scientists working for a common goal.

* Re-written and brought up-to-date from a talk given before the Pharmaceutical Department of the Benares Hindu University, Benares, 1945.

In America, the principle of collaborative research has become the order of the day. Almost all the important drug manufacturing firms have set up their own comprehensive research laboratories where full facilities for team-work between chemists, pharmacologists, pharmacists, bacteriologists and clinical investigators are being offered. Many University authorities are also fostering such a programme within their own staff and are also freely permitting their technical men to work in liaison with scientists engaged in commercial firms for the solution of problems of industrial and applied interest. As a result of such co-operation of the Nation's 'brain-trust', discoveries such as D.D.T. and penicillin, which are of tremendous significance to the health and welfare of the whole human race, have been possible. Prof. J. D. Bernal[1], one of Britain's foremost thinkers, has clearly expressed the significant contributions of 'team research' of to-day in the following words, "Practically the whole of the great advances of science in the 20th century were achieved not by scientists working as individuals, but in organised groups."

The Bottleneck in India

The failure of scientists in India and elsewhere in making worth-while contribution towards this type of progress is largely due to a lack of realization of the benefits of 'collaborative research'. Facilities for research, of course, are generally very limited in a poor country like India and an organization planned on the lines of the Bayer Co. Laboratories and other Laboratories in Great Britain and America cannot perhaps be thought of for many more years to come. But it is indeed a peculiar situation that even the few existing Governmental, University or commercial institutions have not developed any means by which co-operative work would be possible and an interchange of ideas and views effected. This 'closed-door' method is certainly not conducive to progress in any field of investigation, far less in the field of drug researcn where collaborative research is probably much more important to-day than the imagination, initiative and skill of even a gifted but isolated investigator. The bottleneck that exists in this field was strongly voiced in a recent sympossium by a well-known organic chemist of Calcutta, a worker of proved ability and merit and who has been particularly successful in his synthesis of some sulphonamide compounds and who has also made significant contributions in his studies of the coal-tar medicinals including antimalarials of the acridine group. He complained that he could not make any positive statement regarding the efficacy of a new compound of the sulphonamide series which, from all his careful studies pertaining to its chemical constitution and anticipated pharmaco-therapeutical effects, he had reason to believe would prove a boon as a remedy for gastro-intestinal affections of the bacillary dysentry and cholera-type prevalent in India. He had approached several State institutions for a disinterested pharmacologic and clinical study of his product but without success. Either the institutions are too busy with their own work or are not inclined to take up investigational work even on the payment of grants-in-aid or are not permitted by authorities to be associated with work emanating from a commercial firm. The result is that no new remedy, even if it be really worthy, can be presented to the medical profession and people still continue to suffer when much sufferring could probably have been relieved. If adequate pharmacological, chemotherapeutic and clinical trials could not be ensured, the discovery of Sulphonamides and Penicillin would still have remained mere chemical and micro-biological curiosities without the world-wide humanitarian use to which they are now employed.

New Drugs and their Scientific Evaluation

Inspite of the wonderful achievements of modern science it seems impossible to get the public and even some members of the scientific professions to think in scientific terms. The tendency still is to think in terms of the 18th Century rather than of the 2nd quarter of the 20th. During the 18th Century when medicine was pure empiricism, it was not only possible but also probable that the medicinal value of certain new products or a combination of products might be stumbled upon by those untrained and unskilled. That time has passed. Today, while it is theoretically not impossible, it is so improbable that there is no justification in thinking that any Tom, Dick or Harry, with a little tinkering of chemical knowledge or clinical experience, can discover new remedies for the alleviation of human suffering.

As the body of human knowledge broadens and deepens, it becomes increasingly difficult to make any material addition to it, without a very well-conceived and elaborate organisation and a planned attack by really qualified scientists. Such planned attack in the field of drugs must necessarily be tripartite between chemists, pharmacologists and clinicians. It is not a one man's job. The chemists would naturally initiate the attack by elaborating newer and newer compounds on the basis of already aquired knowledge regarding chemical constitution and clinical effectiveness. The pharmacologists must then provide discriminating data on (a) probable toxicity, (b) type and mode of action, (c) worthiness of application to human beings, and (d) reasonableness of replacing existing drugs. Such study requires caution, skill, precision in experimental technique and judgment, which are not easily available in many younger workers. The pharmacologic appraisal, furthermore, is usually a long-drawn and tedious process and, on an average, would require a three-to-one service ratio between pharmacologists and chemists in order to satisfy the needs of the latter. After pharmacological data are complete, clinical trial would always be necessary before any new drug can be introduced to the profession and the public. Otherwise, the clincian would run the risk of endangering human lives if he tries to transfer a new drug direct from a chemical laboratory to the clinic.

Types of Investigation Necessary

It is the general consensus of opinion of modern scientists that all new drugs should pass through several phases of investigation before it is declared suitable for distribution in the open market. It should be studied

in the laboratory and clinically and all investigation should follow a general plan which will permit a thorough understanding both of its usefulness and of its toxic properties. Such a plan has been provided by Winkle, Herwick, Calvery and Smith[2] under authorisation of the Council of Pharmacy and Chemistry of the American Medical Association. This scheme is being briefly presented here with a view to enable all those interested in the evaluation of new drugs to appreciate the complexicity of the task. It will further be of benefit to laboratory workers, pharmaceutical manufacturers, clinicians, pharmacologists, etc.; in fact, to all those who may be called upon to undertake the investigation of new drugs.

Scheme of Study

(*i*) *In the Laboratory:*—

(*a*) Biochemistry—General properties, including solubility and stability; studies of absorption, reabsorption, fate, distribution and excretion; mode of detoxification (excreted, unchanged, oxidised, reduced, acetylated?); effect of enzymes, blood and tissues; chemistry of body fluids and tissues; production of toxic products during course of metabolism.

(*b*) Pharmacodynamics—*Local*: Test of irritation on skin, eye, alimentary canal; intradermal irritation, sensitivity or anaesthesia; tests of protoplasmic depression or toxicity, and reversibility of effects on cilia, nerve trunks, mucosa; haemolysis, antihaemolysis and blood pigment changes. *Systemic*: Action on blood pressure, respiration, muscles, nervous system, cardiac function, secretions, temperature, voluntary activity, organ perfusion, isolated tissues; effects of vasomotor agents, fats, metals, solvents and other agents on the actions of the drug; cumulative effects; development of tachyphylaxis; quantitative and qualitative differences in action in different species of animals.

(*c*) Experimental Functional Pathology—Effect in experimentally induced pathologic states, e.g., smooth muscle spasms, hypodynamic heart fibrillations, and arrhythmias, hypertension, respiratory depression, œdema, shock, burns, anæmias.

(*d*) Chemotherapeutic—effects in preventing specific experimental infections; in combating experimental infections or actions of toxins; antagonists of chemotherapeutic agents, *e.g.*, pus, serum, tissue products; distribution in inflammatory states, *e.g.*, meningitis, dermatitis; minimal effective dosage (ED 50).

To this plan must be added a study of the toxicity of the preparation. This section of the work is important, and covers the study of acute and chronic toxicity of drugs and other chemical agents. The drug will not then be put on the market before the extent of its usefulness and the potentialities for harm are understood. The following outline for such toxicity work is suggested.

(*a*) Acute Toxicity—Dosage reponse curves in three or more species; objective symptoms; statistical calculations for comparative studies; simultaneous comparative determinations of other substances; variations in toxicity with method of administration.

(*b*) Subacute Toxicity—Large daily doses to one or more species for six to twelve weeks; microscopic pathology.

(*c*) Chronic Toxicity—Three or more species; at least one species for the life of the animal; several dosage levels graduated to produce from no effect up to pronounced lesions, and possible shortening of life span; microscopic pathology; effects on voluntary activity, *e.g.*, running or other performance as evidence of more subtle functional changes.

(*d*) Local Effect—Sensitisation; skin irritation; mucous membrane irritation; photosensitisation.

(*e*) Special Studies—Reproduction; distribution and storage; effect of diet; effect of environment; kidney and liver function tests.

There are two important points here—the suggestion of using three or more species in acute and chronic toxicity evaluations, and the proper selection of test animals, which must be carefully done.

At the end of those laboratory observations, a critical review of the accumulated data should be made. The following points should be considered in an effort to reach a decision as to whether a clinical trial of the drug is justified:—

1. Has the drug definite and desirable pharmacodynamic or chemotherapeutic actions?
2. Are its actions constant and reproducible?
3. Are these actions observed in different species of animals?
4. Is the mechanism by which its actions are produced a desirable one, or are the actions the result of an ultimately undersirable reaction of the animal?
5. Are the effects obtained in animals in which experimentally produced pathologic or functional changes comparable to human diseases have been made?
6. What is the therapeutic index of the compound (ratio of effective dose to toxic dose; ED50/LD50)?
7. Are the undesirable side actions of sufficient importance and severity to militate against its clinical use?
8. Is there an adequate margin of safety in its use?

(*ii*) *In the clinic.*

If a clinical trial is indicated, then the primary objectives in this branch should be (1) to determine the therapeutic efficacy, and (2) to detect all signs of clinical intolerance or toxicity. This work must be undertaken by competent investigators in co-operation with the pharmaceutical manufacturer. It is important to select an investigator who has proper qualifications and training in the particular phase of the problem requiring study.

In evaluating the results of the experimental and clinical studies of a new drug, the following factors should be considered:—

1. For what conditions is the drug to be offered?
2. How effective is it in these conditions?
3. Is it superior to other drugs and methods of treatment?
4. What is its inherent toxicity?
5. Does its toxicity outweigh the therapeutic advantages, keeping in mind the seriousness of the conditions for which it is being offered?

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6. If there are other drugs equally or more effective in the same conditions, is the new drug less toxic or does it offer advantages in case of administration, duration of action and so on?
7. How extensive will the use of the drug be; are its applications limited?

'New' Names—Not 'New' Drugs

From the outline for the therapeutic and toxicologic appraisal of new drugs given above, the vast amount of work that is necessary in making a real contribution to this field would easily be appreciated. Though the above scheme of study need not apply in full to all cases, it is considered that the majority of agents should be tested by means such as are described. This might entail in some instances a certain amount of avoidable loss of time, but this is all the more to the good, since recent history contains too many instances of disastrous results that have followed incomplete or inadequate investigation of new drugs.

In countries where the above type of scientific study is not possible, either due to absence of trained personnel or to the lack of a collaborative organisation of different types of technical workers, there is only a very remote possibility of any new discovery in the realm of drugs emanating therefrom. It may almost be taken for granted that claims for any new discoveries from such countries are, more often than not, unreal and based on flimsy grounds which might not stand the test of time. These are mostly discoveries of *new names* for an already known drug or a combination of several known drugs, and not a *new discovery* in the true sense of the word. It is naturally a simpler path for the manufacturers to get their publicity officers to coin a new and catchy name for any nostrum, rather than go to the tremendous expense of maintaining a scientific organisation necessary for the study of synthetic compounds through all their difficult and complex phases, often without any guarantee of their ultimate successful use in medicine. After all, it is known to everybody that out of 100 compounds thus studied, there may or may not be a single worthy compound. More than 1200 compounds were stated to be tested by the German workers led by Prof. Schulemann, the pharmacologist, before plasmochin and atebrin could be discovered. The odds are therefore heavy against financing of drug research and only high idealism, associated with a full realisation of the benefits that might accrue to mankind in the event of even a chance success, can make such efforts possible. If success comes in the way, the undertaking of such research may prove a sound business proposition and this has actually happened in more than one instance, but the latter should not serve as the only objective.

Possibility of Setting up Drug Research Organisation in India

In Germany, the necessary idealism and the spirit of adventure in the quest for the unknown were provided more than 40 years ago by a commercial concern, the Bayer Remedies, a concessionary of the I. G. Farbenindustrie Aktien-Gesellschaft. It is remarkable that at the time when Bayer Co. organised their collaborative research programmes, the German academic faculties, inspite of their high scientific attainments in pure researches in chemistry and pharmacology, could not appreciate the tremendous significance of this type of applied research, and there is no record to indicate that the State authorities financed any similar studies in the various German academies. In Great Britain and America however, support for such research came freely from the State on the one hand and from private endowments and commercial enterprises on the other. As a result of this new attitude to drug research, marvellous results have been achieved in the elaboration of the newer sulphonamides, penicillin, D.D.T., Gammexane, and a host of lesser known but equally significant remedies. America is making a quick march in this direction because munificent private donations from bodies such as the Rockefeller Foundation, etc., are easily forthcoming for research projects along with research grants from the American National Research Council. There is today no drug manufacturing firm worth the name in America which does not maintain a first-class research laboratory and a team of research workers. In addition, many firms support research work in University and Hospital centres by lump grants or through fellowship projects.

The same story can be repeated in India, possibly with equal amount of success, if there is only the *will* to do it. It is not the lack of scientific talent which is standing in the way, but the set-up of a really collaborative drug research organisation. The establishment of a National Institute for Drug Research where botanists, chemists, pharmacologists and clinicians would be able to join their heads and hands together in an effort to find out a new remedy either from vegetable, animal, mineral or synthetic sources has been suggested by the writer[3] and has met with the approval of many medical and scientific organisations in this country. If private munificence and State aid are forthcoming, as is likely during the post-war period, such a project need not necessarily prove to be an ideal dream.

Pending the establishment of such a machinery, there seems a clear need for a re-orientation in outlook of some of our leading Indian Universities and State research institutions towards collaborative applied research. In University circles, there is often lacking that spirit of co-operation between several class of research workers, which might ensure a thorough checking of the products of their organic chemical laboratories. Departmental prestige and departmental output of research is often sedulously fostered, and this prevents any so-called 'outside' work being accepted. Friendly relations between departments and commercial research units in drug manufacturing firms are not often generously followed with the result that cross-fertilization of ideas, which are sometimes the foundations for 'creative' work (as distinguished from routine detail work), is never made possible. As matters stand at present, State institutions are the only centres where disinterested pharmacotherapeutic testing of new drugs is possible and positive collaboration from such centres should be freely forthcoming. Clinical research is

being supported by the Indian Research Fund Association and before long the crying need for clinical testing of drugs may perhaps be met to a certain extent. The urgent need now is for more 'Research Hospitals' where controlled clinical investigations could be conducted. Alternatively, 'research wards' could be set apart in public hospitals where members of the Pharmacology and Medicine faculties of the Medical Colleges would be free to conduct their investigational work.

The Role of the Drug Manufacturing Firms

To the drug manufacturing firms, medicine owes a great debt in assuming heavy financial risks in the promotion of new medicinals. Commercial firms, such as the Bayer Company in Germany, the Sandoz and the Roche Co. in Switzerland, the Burroughs Wellcome Co., British Drug Houses, May and Baker Co., etc., in England, the Lilly Laboratories, the Squibb Research Laboratories, Parke, Davis & Co., and others in America have enriched therapeutics by worthy contributions. They have supported teams of workers, sometimes for years together, in the hope of making new discoveries and their efforts have not been in vain. In fact, in drug research, more than in any other field, the contributions of the commercial firms rank on a higher level than that of University and State Research Institutions.

If India wishes to play a similar role, the drug manufacturing concerns must assume leadership in this line and start in right earnest to create their *individual* research laboratories on the 'team' principle or where financial obligations would not permit, *group* laboratories, jointly supported to cater for the needs of their supporters. Alternatively, the Indian Chemical Manufacturers' Association, which represents the majority of Indian chemical and pharmaceutical manufacturers, may be asked to set up a control and research Laboratory on the lines of the Laboratory maintained by the American Drug Manufacturers' Association. Barring the right type of scientifically minded clinical investigators (which are unfortunately not many in India, as medicine is still being practised as a *profession* and not as a *science*), almost all other types of workers, e.g., synthetic chemists, botanists, pharmacologists, bacteriologists, etc., would now be available in this country. A start must be made and only then would the right type of personnel be forthcoming. Once the realization comes of the benefit of such collaborative research, private institutions of the type of Mellon Institute at Pittsburg and the Nuffield Institute at Oxford would not be long in coming in India.

It is a happy augury of the times that a distinct awakening towards promotion of research by commercial firms is making itself evident in India. There are at least two firms in Calcutta* and one firm in Bombay† which are systematically suporting research in their own Laboratories. There may be others with which the writer is not acquainted. One of these firms has gone so far as to offer research grants to Government institutions and University Laboratories towards the furtherance of pure research, unconnected in any way with their own manufacturing problems. Recently, this firm has produced a report of research work carried out under the guidance of its Research Association, which provides a stimulating reading and indicates a proper appreciation of the requirements of drug research work. It is certainly going ahead in the proper direction and setting an illustrious example for others to follow. Only by such ways and through year-to-year painstaking and systematic study can India hope to figure in the scientific world and discover new remedies for the cure and alleviation of many diseases peculiar to her soil. There is no royal and easy road. No specific 'cure' (other than 'faith cure', of course) can suddenly be discovered through a flight of imagination. True, discoveries are often products of 'chance', but such 'chance' comes only to those who are in the thick of the fight and who are trained to recognise it.

†Alembic Chemical Works, Bombay.
*Bengal Immunity Co. & Bengal Chem. Pharm. Works.

Summary

Discovery of new drugs, once an open field for all newcomers, is today becoming more and more a matter calling for the most intensive special qualifications. Further, it needs, in addition, a collaborative effort between various types of scientists of the best calibre. The secret of success of countries such as Germany, Switzerland, Great Britain and America in elaborating new drugs for specific therapy is found on ultimate analysis to be a collaborative effort between chemists, pharmacologists, and clinicians. Such collaborative effort has been made possible in Germany and Switzerland through enterprising and far-seeing commercial concerns and in Great Britain and America through State help, private endowments, and also the support of commercial concerns. In drug research, the objective should primarily be towards discoveries for the benefit of the human race, and only secondarily to financial considerations. Immediate results should not be expected, as sometimes long-drawn and painstaking work has been productive of no significant results. However, the success that has already been achieved proves without doubt that further success should not be beyond the reach of any honest group of investigators. India and many other countries have remained backward in this type of work. This backwardness is probably not so much due to the lack of talented scientific personnel as to lack of a collaborative organisation and joint efforts. Provided the will and leadership is available, India can figure in this field of research by developing better cooperative work between existing institutions and stimulating more research efforts in commercial concerns. There seems to be an awakening in this direction as a result of the second world war, and the present time seems to be most opportune to go ahead with elaborate and comprehensive schemes. Money spent will not be lost, but may come back in the form of better national health and national fitness.

References

[1] Bernal—*New Statesman*, Feb., 24, 1940.
[2] Winkle, Herwick, Calvery and Smith—*J. A. M. A.*, **126**:958, 1944.
[3] Mukerji—Presidential Address, Indian Sci. Cong., Physiol. Sec. Nagpur, 1945; *Calcutta M. J.*, March, June, July and Sept., 1945.

MALARIA TOXIN AND ACTION OF QUININE IN CLINICAL MALARIA

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Malarial ague has long been known to start simultaneously with the breaking up of the rosettes. These rosettes liberate besides the young merozoites, hæmozoin pigments. It has been asserted that a toxin is also liberated at the same time; and it is this toxin which gives rise to the clinical symptoms. The nature of this toxin has not yet been determined, but the ague simulates hæmoclastic shock caused by sudden liberation of toxin. Rosenau and others by injecting filtered serum procured during the cold stage have been able to demonstrate its presence (Manson, 1917). However, this particular toxin has not yet been identified.

The hæmozoin pigments are more or less extensively distributed throughout the body. They have been found in the brain and spleen after death from cerebral malaria even when no parasites are present (Viswanathan, 1944). In fact their presence in the body without the parasites is evidence of recent malaria. These granules are found wherever there is any pathological lesion. A lesion is seldom found without the simultaneous existence of these pigments. They are almost co-existent. The degree and extension of pigmentation as well as those of the retrograde changes in the tissues and organs largely depend upon (1) the type of infection, (2) its virulence and (3) the distribution of parasites (Solis-Cohen and Solis-Cohen, 1916). These pigments are distinguishable from those found in other diseases by being both extra and intravascular.

It has been observed that as soon as the hæmozoin pigments are delivered into the liquor sanguinis they are vigorously attacked by the leucocytes which have been found to increase even upto 30,000 in cases of severe infection (Manson, *loc. cit.*) Leucocytosis occurs during paroxysm (Stitt, 1922, Megaw, 1942; Manson-Bahr, 1944). These attacks go on everywhere in the body in the circulation, spleen, liver, intestine and in fact in every part of the body where the pigments gain access. 'The splenic vein direct from a rich breeding ground contains a large number of hæmozoin-laden leucocytes' (Manson, *loc. cit.*).

These pigments have been regarded by Manson as 'specific product' of the malaria parasites themselves. Banerjee and Bhattacherjee (1943) think that they have a toxic action which produces cloudy swelling and degeneration of the phagocytic cells. Viswanathan (*loc. cit.*) found degeneration of endothelium, the cells of which contained pigments. Hæmozoin may act as hæmolysin (Manson-Bahr, *loc. cit.*). Stitt (*loc. cit*). thinks along with Brown that they can also bring about degeneration of the endothelial cells by being taken up by them, with associated capillary hæmorrhages. The toxic nature of the pigments may also be deduced from their behaviour prior to the rupture of the red cells. The segmenting schizonts except in cases of *P. vivax* are never big enough to so distend the walls of the red cells as to cause their rupture. It seems more probable that the walls get disintegrated through the action of the toxin liberated from the pigments. As the schizonts begin to segment the pigments, which were located mainly at the periphery, are discharged from the body of the parasites and occupy a central place surrounded by the segments so that their toxin may not act prematurely on the cell walls before the merozoites are fit for liberation. When the merozoites are completely separated from one another, toxin from the central accumulation of pigments reaches the wall through the channels running between the segments, and disintegrate it in the same way as the endothelial cells are disintegrated. As a result the merozoites are liberated into the liquor sanguinis.

Leucocytes are considered to be the advance-guards, the first line of defence, against invading forces. From the beginning of invasion, that is, the onset of clinical symptoms these advance-guards attack the hæmozoin pigments to the exclusion of the parasites, which are seldom phagocytosed in the peripheral circulation. Therefore these pigments must be considered to be of primary importance among the invading forces. They persist even after the parasites have disappeared from the body, and disease continues sometimes culminating in the victory of the invaders. Or again the fight continues to such a pitch that the parasites too are attacked in the peripheral circulation as in Das Gupta and Ganguli's case (1944). But here again the schizonts only are phagocytosed to the exclusion of the rings and gametocytes although these latter are much smaller in size. The rational explanation of such a phenomenon lies in the fact that neither the rings nor the gametocytes are of importance, since they are not likely to supply reinforcement soon for a fresh onslaught, while the natural function of the leucocytes tells them that the schizonts have been bringing fresh contingent for the fight and must be destroyed forthwith without giving the enemy an opportunity to start the fight over again. The rings are hyaline bodies and do not contain pigment until they are fairly developed, neither are they likely to deliver the pigments, and so do not provoke the leucocytes to action. Similarly, the gametocytes, though they contain a few pigments, are not likely to set them free and cause mischief. Consequently the leucocytes do not take any notice of them. Perhaps herein lies the secret of relapse even in adequately treated cases. It is not the parasites 'lurking in the cells of the reticuloendothelial system' that escape from the action of quinine, since it never had any action on them, but that they being innocent do not stimulate the system to phagocytic action.

Hæmozoin pigments are, therefore, the repository of the toxin which produces pathological changes in the body giving rise to different symptoms in connection with malaria. In the blood it causes destruction of the platelets (Beattie and Dickson, 1921) and the red cells not attributable to the direct action of the parasites. In the spleen it causes thrombosis and focal necrosis (Solis-Cohen and Solis-Cohen, *loc. cit.*), liver hepatitis, kidney nephritis, in the brain the varied symptoms according to the particular area affected, and so on. In the vessels it produces pathological changes in the

endothelium. Blocking, which is considered to be the cause of the cerebral symptoms, is secondary to these degenerative changes as suggested by Viswanathan (*loc. cit.*). Presence of parasites, according to him, inside or outside the cells is immaterial so far as clumping is concerned. Emboli are not found in the hyperpyrexial and hæmorrhagic malaria (Magaw, *loc. cit.*). Sinus thrombosis observed by Viswanathan was probably caused by dangerous fall of blood pressure due to large doses of quinine given intravenously. He did not find the pressure below normal in any of those cases before the commencement of treatment. Unfortunately he does not state the record of pressure during the course of treatment. Lack (1943) from observation on infected canaries found transient sticking of leucocytes to the endothelial lining of the venules plus evidence of plasma leakage, followed later by clumping of both infected and healthy cells, retardation of the rate of flow and pastelike flow of blood. There must have been some damage of the endothelial cells to account for the sticking of leucocytes. Viswanathan found no evidence of inflammation or necrosis of the brain. 'Intravascular thrombosis and consequent avascularization' according to him 'is the cause of malarial coma and death'. Punctiform and other hæmorrhages are probably due to deficiency of blood platelets and damaged endothelial cells.

Devine and Fulton (1941) found the crude hæmozoin pigments to contain only about one sixth of hæmozoin, which is chemically and spectroscopically indistinguishable from hæmatin, and the rest primarily of 'parasitic protein' which remains undissolved round the pigment granules. This protein envelope seems to be the toxic product of the parasites. It may be that a part of it goes into the circulation from which Rosenau and others could demonstrate its presence.

Therefore, it is the toxin and not the parasite that is of prime importance. And the pigments are store-houses of this toxin.

Having established this let us see how quinine acts in effecting cure of clinical malaria. Opinion differs regarding its mode of action in malaria. There are several views which may be summarised as (1) direct action on the parasites and (2) indirect action on them through the defensive mechanism of the body. Quinine disintegrates plasmodium *in vitro* in a concentration of 1 in 10,000. But this concentration is never reached in human blood; in fact it never exceeds 1 in 100,000; besides it is rapidly excreted, 90% disappearing within a minute after intravenous injection (Ghosh, 1944); Morgenroth (1918) found the quinine content of the blood to be 1 in 20,000 a few minutes after intravenous injections and 1 in 150,000 after oral administration of therapeutic doses. 'Part of the drug is deposited in the spleen, liver and other organs in an inert form' (Megaw, *loc. cit.*). Maximum concentration is retained in the human blood for only half an hour (Chopra *et al*, 1934). To maintain a steady maximum to be effective, if it is effective at all, against the parasites quinine has to be given every half an hour which is never done. Therefore, owing to low concentration, rapid elimination and partial transformation it cannot act as a parasiticide in the human body. De Sandro (1909) says, 'most of the quinine injected (hypodermically) is found in the spleen where it reaches after an interval of fifty minutes, and it remains there longer than in any other part of the body and can be demonstrated even twenty-four hours after the injection'. But in spite of this the parasites accumulate and remain there for a pretty long time and produce relapse. It can neither prevent infection even when the blood is saturated with quinine (Megaw, *loc. cit.*). If quinine had acted as a parasiticide within a minute after an intravenous injection a large number of parasites should have been destroyed. But on the contrary in Gavan Duffy's (1944) case we find the parasites increase by 150% after 16 grains had been administered intravenously. Similar increase has also been observed by Chopra and others (1932). Again their rapid destruction should have been followed by aggravation of symptoms owing to sudden liberation of a large amount of toxin. This, however, never occurs. Small doses of quinine quite incapable of destroying parasites, of course, sometimes wake up latent malaria and bring about an ague. But this may be explained by the fact that such doses by causing contraction of the spleen (Cushney, 1936, Ghosh, *loc. cit.*) squeeze out the parasites. I am in the habit of giving parenterally 10 grains of quinine without any stimulant and repeating it after two hours, sometimes 20 grains in a single dose in apparently hopeless cases of algid or choleraic malaria with dramatic effect. Less than 10 grains in a dose is never given whether the patient is 30 years or 30 days old. The pulse appears at the wrist, temperature rises and evacuation stops within a very short time. Hundreds of such cases have been treated with uniform success. No aggravation of symptoms nor any depression of the cardiovascular system has been noticed. Intramuscular route is invariably used. Megaw's charts also show how quick and large doses act rapidly in controlling pulse and temperature, while small and leisurely administration delays action sometimes with disastrous result.

To clear up this confusion different workers offer different explanations none of which is, however, convincing. They are (1) that quinine acts on the merozoites but not on the sporozoites; (2) that the mature schizonts but not the rings are affected; (3) that it acts by making the red cells impervious to the merozoites; (4) that it makes the red cells more pervious for the 'all sufficient' serum to act on the parasites within the cells. There is no reason why it could not destroy the sporozoites; both are extra-corpuscular, of the same nature and constitution though different in shape and origin, and both enter the red cells and develop into rings. Similarly, the schizonts and rings are of the same constitution and intracorpuscular. If one is affected why not the other? Again if a coating on the cell wall can prevent entrance why can it not prevent egress as well? In birds inoculated with *P. Gallinaceum* intense quininization could not prevent the merozoites from entering the red cells, neither could it destroy the parasites, which not only survived in liquor sanguinis saturated with quinine but thrived and multiplied as well. The only thing quinine could do was to arrest the growth of intracorpuscular merozoites

and keep the erythrocytic schizogony of pigmented form in abeyance so long as quinine is in sufficient concentration in the blood (Adler and Tchernomoretz, 1941, 1943). Some ingredient in liquor sanguinis which is essential to the growth of the parasites is prevented by quinine from reaching the intra-corpuscular merozoites. The inevitable conclusion, therefore, is that quinine does not cure malaria by destroying the parasites.

As regards the second view, phagocytosis of plasmodium undoubtedly occurs both in the peripheral blood as well as in the spleen; but symptoms persist even after complete disappearance of parasites in cases where sufficient quinine has been given for a pretty long time (Viswanathan, *loc. cit.*). Besides prolonged administration of quinine often fails to completely liquidate the parasites and prevent relapse. Moreover, quinine causes a preliminary leucopenia before increasing the leucocytes (Ghosh, *loc. cit.*). Should not therefore, there be an initial aggravation of symptoms? Das Gupta and Ganguli's (*loc. cit.*) case put up a heroic fight even in a starving condition without the aid of quinine before yielding to the enemy. He was a destitute wandering in the streets of Calcutta for a morsel of bread and could not possibly have any quinine which was then selling at one rupee a grain. Even such extreme phagocytosis of parasites as observed by them did not require the help of quinine, neither could it save the patient. So quinine does not cure malaria through phagocytosis.

How then does it act? It acts on the immediate cause of the symptoms thereby relieving them. If toxin is the cause of the symptoms, and there could be no question about it, quinine must act on this toxin. Phagocytes devour the parasites and the pigments, but they cannot destroy the toxin. Quinine does it.

Gupta and Ganguli (1944) found that malaria-infected monkeys tolerated much bigger doses of quinine than noninfected ones. In fact they required higher doses to save themselves. They think that it is absorbed by the parasites thereby relieving the cells of the hosts from its toxic action. If quinine could be absorbed by the parasites how could extra erythrocytic multiplication be possible in the experimental birds of Adler and Tchernomoretz? Where then does this excess quinine go? Howie and Murray-Lyon (1943) observed that in acute subtertian malaria when quinine was not excreted in any urine the condition of the patient remained grave and could only be improved by injecting more quinine intravenously when the drug was detected in the urine as well. Again those who excrete the drug regularly improve rapidly. Ordinarily about one-third of the quinine absorbed appears in the urine (Cushney, *loc. cit.*). Where then does this lost quinine go? What is it required for? Kelsey and Oldham (1943) from studies on quinine oxidase in the tissues found some activity of this enzyme in human liver. During an attack of malaria this activity may be increased and be responsible for the disappearance of the quinine. Gupta and Ganguli (*loc. cit.*) do not consider it likely that the destruction is greatly accelerated by the malarial infection. However, if there is greater destruction, or shall we say utilization, there is greater requirement as well, in such cases. The efficiency of the reticulo-endothelial system as measured by the congo-red index is increased in infected monkeys where infection is controlled by quinine and the general condition improved (Gupta and Ganguli, *loc. cit.*). This increased efficiency is probably due to the elimination of the toxin by quinine, since in unchecked malaria this efficiency is diminished, apparently due to the deleterious action of the increasing amount of toxin liberated by the increasing number of parasites on the system. So it is not the parasite that absorbs it, neither does the red cell absorb it, nor is it destroyed by the enzyme merely for the sake of destruction. It renders the toxin innocuous either by adsorption or by some delicate chemical reaction with it. The result is that neither quinine nor the toxin is capable of exerting its individual specific influence on the host. When sufficient quinine is not given to neutralise the whole of the toxin there is no surplus left to be excreted, and the action of the unaffected part of the toxin persists. To be spared for excretion after neutralizing all the toxin, more than sufficient should be administered, when both improvement of clinical condition as well as Tanret reaction are obtained. A third condition may be possible where the quantity of quinine is nothing more nor less than what is absolutely necessary for complete neutralization of the toxin. Here no quinine will be detected in the urine, but the disease will be cured. Since it is impossible to measure the quantity of the toxin it will be a mere chance when this state would be obtained. If the target is not known the bullet will more often than not fall short of the mark or pass beyond it. An ideal dose would be one which leaves a constant trace of quinine in the urine throughout the course of acute attack and gives a faint Tanret reaction. If administration of quinine is stopped before the defensive mechanism of the body is sufficiently developed early relapse is likely; for, we find the dormant merozoites in the red cells developing into schizonts when quinine is eliminated or its concentration in blood is sufficiently lowered (Adler and Tchernomoretz, *loc. cit.*)

The questions that can arise in connection with the action of quinine are, (1) how could infected monkeys tolerate more quinine than what would otherwise have killed them, (2) why quinine sometimes fails to appear in the urine during the course of treatment in acute malaria, (3) why should bigger doses be required by children than their age and weight call for, and (4) why prophylactic use of quinine cannot prevent relapse?

If we accept that quinine acts as an antitoxin all these points can be satisfactorily explained. More quinine is tolerated because the excess is required to neutralize the toxin thereby relieving the cells of the host from its toxic action. Secondly, quinine fails to appear in the urine because of the change in its constitution in the process of neutralization of the toxin. As regards the third point, children have not acquired any immunity which can at least partly control the toxin as happens with the adults; besides the average number of parasites in their blood is about one hundred times that of adult in the same endemic area (Napier, 1943).

Hence more quinine is required to neutralize unaided the greater amount of toxin liberated. Fourthly, relapse cannot be prevented even after administration of quinine in prophylactic doses extending over a period of even twelve months; in fact after the stoppage of the prophylaxis the incidence of relapse is actually higher than in those receiving no prophylactic treatment (Field, Niven and Hodgkin, 1937). This is due to the fact that while quinine could not eradicate or prevent entrance of parasites, by constant presence in the blood it neutralises the toxin whenever it is liberated by the parasites. Absence of free toxin in the system prevents the growth of immunity in the host. Consequently when the drug is withdrawn relapse occurs uncontrolled by any immunity. So from whatever angle it is seen the only possible conclusion is that quinine acts as an antitoxin.

Summary and Conclusion

Pathology of malaria and its relationship with the hæmozoin pigments are discussed. Hæmozoin pigments are the repository of the toxin which produces the morbid changes giving rise to the varied symptoms of clinical malaria.

Fallacies of the current views on the action of quinine in malaria are pointed out and a new theory, that quinine acts as an antitoxin by combining with the toxin whether by adsorption or by some other delicate chemical reaction is enunciated.

My thanks are due to Mr. S. Neogi, M.SC., Khulna, and my nephew Mr. J. C. Das Gupta, M.SC., of Messrs Bathgate & Co., Calcutta, for the great encouragement and suggestions received.

References

Adler, S. and Tchernomoretz, J.—*Ann. Trop. Med.*, **35**:241, 1941.
Idem—Ibid, **37**:148, 1943.
Banerjee, J. C. and Bhattacherjee, P. B.—Hand Book of Tropical Diseases. U. N. Dhar, Calcutta, 1943.
Beatie, J. M. and Dixon, W. E. C.—A Text Book of Special Pathology. Published by W. Helnemann, Ltd., 1921.
Chopra, R. N., Roy, A. C., and Das Gupta, B. M.—*Indian M. Gaz.*, **69**:10 & 560, 1934.
Chopra, R. N., Das Gupta, B. M., and Sen, B.—*Ibid*, **67**:680, 1932.
Cushney, A. R.—Pharmacology and Therapeutics, 1936.
Das Gupta, B. M., and Ganguli, S. K.—*Indian M. Gaz.*, **79**:10, 458.
De Sandro—Reforma Medica, Nov. 8, 1909, quoted by Sajous in his Analytical Cyclopedia of Practical Medicine, Vol. III, 1916, p. 367.
Devine, J. and Fulton, J. D.—*Ann. Trop. Med.*, **35**:15, 1941.
Dixon, W. E.—A Mannual of Pharmacology. Edward Arnold & Co., London, 1936.
Field, J. W., Niven, J. C. and Hodgkin, E. P.—League of Nations: Bull. Health Organisation, **6**:236, 1937.
Gavan Duffy, C. A.—*Indian M. Gaz.*, **79**:5 & 211, 1944.
Ghosh, B. N.—Pharmacology, Materia Medica and Therapeutics, Hilton & Co. Calcutta, 1944.
Gupta, J. C. and Ganguli, S. C.—*Indian M. Gaz.*, **79**:3 & 104, 1944.
Howie, J. W. and Murray-Lyon, R. M.—*Lancet*, **2**:317, 1943.
Kelsey, F. E. and Oldham, F. K.—*J. Pharmacol. & Exper. Therap.*, **79**:77-80, 1943.
Lack, A. R. Jr.—*Science*, **96**:520, 1942, abstract by *J.A.M.A.*, **121**:148, 1943.
Manson-Bahr, P.—Synopsis of Tropical Medicine, 1944.
Manson, P.—Tropical Diseases, 1917. Cassell and Co., Ltd., London.
Megaw, W. D. and Rogers, L.—Tropical Medicine, 1942.
Morgenroth, J.—*Deut. med. Wochnschr.*, **44**:961 & 988, 1918, quoted by *Indian M. Gaz.*, **69**:10 & 561, 1934.
Napier, L. E.—The Principles and Practice of Tropical Medicine Part I, Thacker Sprink, Calcutta, 1943, p. 69.
Solis-Cohen, S. and Solis-Cohen, L.—Sajou's Analytical Cyclopedia of Practical Medicine, 1916, Vol. VI; 503.
Stitt, E. R.—The Diagnostics and Treatment of Tropical Diseases, 1922.
Viswanathan, R.—*Indian M. Gaz.*, **79**:10 & 455, 1941.

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The secondary anaemia rapidly clears up with iron, while the appetite may have to be stimulated in some cases with the help of stomachics. The diet should be ample and nutritious.

Acknowledgement

My grateful thanks are due to my chief, Prof. Sahai for helpful advice, and to Dr. Akhtar Husain of Fyzabad and Dr. J. K. Das of Lucknow for referring some cases to me.

References

Frimodt-Möller and Barton—*Indian M. Gaz.*, **75**:607 1940.
Weingarten—*Lancet.*, **2**:103, 1943.
Treu—*Indian M. Gaz.*, **78**:70, 1943.
Simeon—*Ibid*, **78**:271, 1943.
Choudhri—*Ibid*, **78**:575, 1943.
Chakravarty—*Ibid*, **78**:596, 1943.
Shah—*Ibid.*, **78**:597, 1943.
Greval—*Ibid.*, **78**:676, 1943.
Gupta—*J. Indian M. A.*, **14**:102, 1945.

N.B.—This papers was written in Feb., 1944. Since then, over a dozen other cases have been seen by me, and a couple of previous cases have returned with a relapse.

A peculiar feature seems to be the apparent frequency with which medical men get these cases, the probable explanation being that they are more carefully investigated.

Another important point is the optimistic note of the original article, wherein it is suggested that intravenous arsenicals effect a quick and complete cure. This optimism has not been justified by subsequent experience. Relapses have been found to be not infrequent, and more than one case of apparently true Benign Eosinophilaemia has either not responded at all or only poorly with arseno-therapy.

(*Continued from page 47*)

Acknowledgment

My thanks are due to Major-General H. C. Buckley, M.D., F.R.C.S., C.S.I., I.M.S., Principal, Medical College and Superintendent, Thomason Hospital, Agra, for his kind permission to publish the record of the case.

References

Clark, J. T.—*J. Trop. Med.*, **15**:133, 1912.
Deeks—Quoted in Editorial, *Indian M. Gaz.*, **77**:545, 1942.
Editorial—*Indian M. Gaz.*, **77**:546, 1942.
Giglioli, G.—Malarial Nephritis, J. & A. Churchill, London. 1930.
Heilig, R.—*Indian M. Gaz.*, **76**:519, 1941.
Idem—Ibid., **77**:513, 1942
Laha, P. N.—*Ibid.*, **80**:135, 1945.
Manson-Bahr, P. and Maybury, L. M.—*Trans. Roy. Soc. Trop. Med. and Hyg.*, **21**:131, 1927.
Marchiafava and Bignami—Quoted in Editorial, *Indian M. Gaz.*, **77**:545, 1945.

IDIOPATHIC PULMO-EOSINOPHILAEMIA

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Historical

Considerable interest has been aroused in this country since the publication in 1940 by the late Frimodt-Möller and Barton (1940) of 175 cases with a symptom complex which they, rather unfortunately, labelled 'pseudo-tuberculosis with eosinophilia'. This symptom-complex was selected out of a total number of 5,500 cases which passed through their hands in the Madanapalli Sanatorium, Madras, between 1925 and 1940. These cases were sent to them as cases of pulmonary tuberculosis with low fever, cough with expectoration, occasional haemoptysis, loss of weight, characteristic x-ray picture and marked eosinophilia, but the sputum was consistently negative for tubercle bacillus. They did not suggest any particular line of treatment but stressed its nonspecific and benign nature.

Later, Weingarten (1943), under the heading 'tropical eosinophilia', reported 81 cases observed in Bombay between 1933 and 1942. He found spleen enlargement in a large number of cases during the acute and subacute phase and reported the 'happy' coincidence of a patient, under observation for the above condition, contracting syphilis for which he was treated with neoarsphenamine, which not only cured his syphilis but also the eosinophilic state. In view, however, of the report of Greval (1940) and Gupta (1945) who found a positive W.R. (but negative Kahn test) in some cases of eosinophilia in the absence of any history or other signs of syphilis, one wonders whether Weingarten's case was really suffering from syphilis also.

Treu (1943) from Calcutta reported two cases, one of whom was cured by a few doses of acetylarsan, while the other got pneumonia, which cleared off the eosinophilic state.

Simeon (1943) from Bombay reported 35 cases in 9 years and found spleen enlargement in 50 per cent of cases and suggested the name Benign Eosinophilic Leukæmia, which seems as unhappy a choice as that of Frimodt Möller's because leukaemia is an universally fatal condition*.

Chaudhry (1943), Chakravarty & Roy (1943) and Shah (1943) reported one case each.

My interest was attracted when I saw a case, about 14 months ago. This patient had been diagnosed as suffering from pulmonary tuberculosis and had been sent to a sanatorium where he stayed for 4 months without any benefit. He had low fever, spasmodic cough with scanty expectoration for about 14 months, occasional slight hæmoptysis, loss of appetite and weight. Clinical examination showed a pale and thin young man of 28 years, with generalised signs of bronchitis, harsh breath sounds with a few rhonchi and medium crepitations persisting after cough. The signs were more marked on the left midzone. The sputum was persistently negative for tubercle bacillus (even by the concentration method), though it showed a large number of eosinophils, while the x-ray showed generalised fibrosis with diffusely scattered infiltrations suggesting submiliary tuberculosis or pneumokoniosis. The blood count showed a fair degree of microcytic anæmia, while the total white blood cell count was 23,000, and the differential count showed eosinophils 70 per cent. The spleen was not palpable, though he came from a zone of endemic malaria (Gorakhpur District). He had never been near the sea. There was no previous personal or family history of asthma, though the coughing at times became paroxysmal in character. He was put on a stimulant expectorant mixture. In addition he was given intravenous injections of "soamin"—a pentavalent arsenical, the first dose being gr. i, dissolved in 2 c.c. of sterile distilled water (to test his sensitivity to arsenic) and subsequently gr. iii in 5 c.c. of sterile distilled water given twice a week for 3 weeks (a total of 19 grains). He made an uninterrupted recovery, became afebrile and put on weight. His cough disappeared and the blood count returned to normal level. Unfortunately a second x-ray could not be taken. He went home just a year ago and has maintained good health.

Since then 7 more cases have been seen and the following account is based on them, and on the literature available on the subject.

Definition

A symptom-complex characterised by a long chronic duration and more or less benign course with low fever, cough (which may be occasionally spasmodic in character), scanty expectoration, occasional hæmoptysis, loss of weight, marked relative and absolute eosinophilia, characteristic x-ray appearances and showing a dramatic response to intravenous arsenotherapy. Various names have been suggested. Frimodt Möller's 'pseudo-tuberculosis' is a very unfortunate choice because of the tragic association with tuberculosis. Weingarten's 'tropical eosinophilia' is not so bad, but seems to suggest an artificial geographical narrowness which may not be correct. Simeon's 'benign eosinophil leukæmia' is also unsuitable because leukæmia is always associated with a fatal ending. The author suggests the name 'idiopathic pulmo-eosinophilæmia'.

Aetiology

No age seems to be exempt. The youngest case seen by me being only 2 years old, while the oldest was over 50 years of age. Both sexes are prone to it, as also all strata of society. Weingarten suggests some correlation with the seaside, but none of my cases had ever gone beyond the U.P. There appears to be a special seasonal prevalence, the condition being more common during the cold season. Diet, alcohol, tobacco, colour of the skin (white, brown, or black) show no significant association and no history of past illness appears to be of any importance. No autopsy has yet been made on any case of this disease.

Symptoms and Signs

Some cases seem to have an acute onset with fever going upto 101-102°F, followed a few days later

* Simeon was partly justified in using the term leukæmia because he had qualified it by the prefix 'benign'.—Editor, *J.I.M.A.*

by troublesome cough which tends to be spasmodic at times and may resemble a mild attack of asthma. Enlargement of spleen has been reported in many cases by Weingarten and Simeon though this is not my experience. After some time, the fever tends to go down and a chronic phase is entered, which may last for a long time. Many patients say that the onset was like an attack of coryza—a mild 'influenza'—which later became chronic. In the majority, an insidious onset is observed with low temperature, troublesome cough, which gets worse as time passes, and is often frankly spasmodic in character with audible wheezing. The sputum is scanty and mucoid and not infrequently frankly blood-stained. Gradual loss of appetite, loss of weight and increasing weakness and pallor are observed. Sleep is much disturbed by cough which is specially troublesome at night.

Physical examination shows the patient to be thin (with definite loss of weight) and anæmic. The temperature varies between 99 and 100°F. The pulse is rather rapid. Weingarten and Simeon have described a well marked splenomegaly during the acute and subacute phase, but I have not yet observed this sign.

The chest is bilaterally symmetrical with equal movement on both sides. Vocal fremitus is unaltered while the percussion note tends to be hyperresonant. Auscultation reveals harsh breath sounds with prolonged expiration, many bronchi in the early stages, which are later replaced by medium crepitations which persist after coughing. Vocal resonance shows no change. Sputum will always be found negative for tubercle bacilli, but contains the usual bacterial flora and a large number of eosinophil cells, but Charcot-Leyden crystals and Curshmann's spirals have not been reported. Several workers have recently reported the finding of mites in the sputum of their cases and attach a causative significance. Sputum examinations in the recent cases have been persistently negative for mites. Blood examination reveals a moderate degree of secondary anæmia, but the most characteristic feature is marked leucocytosis which may vary from 20,000 to over 100,000 cells per c.mm., while the absolute numbers of the neutrophils and the lymphocytes are usually unaltered. Simeon comments on the very 'mature' and multinucleated character of the eosinophil cells. The x-ray examination reveals a startling condition, very suggestive of miliary or submiliary tuberculosis or pneumokoniosis. In other cases the lungs present a marked degree of diffuse fibrosis.

Diagnosis and Discussion

The diagnosis is not difficult if the condition is kept in mind in all cases of persistent cough. This is helped by the examination of a blood film. Miliary tuberculosis is a very much more acute condition and is invariably fatal within a few weeks. Considerable difficulty may be experienced in separating this condition from bronchial asthma, but the paroxysms are much less severe (though relieved by adrenalin and ephedrin), while in asthma the blood count is seldom over 15,000 and the eosinophils are under 20 per cent and there is no febrile reaction. Moreover, no case has been reported from Europe, where asthma is common. From chronic bronchitis, the differentiation is only possible by the examination of a blood film; this will also exclude pneumokoniosis or syphilis of the lung. Loeffler's syndrome is somewhat like this, but its duration is only for a week and it is a self-curing condition.

The other conditions which produce eosinophilia are anaphylactic states, certain skin diseases and helminthic infestation of the bowels, but in these conditions the eosinophils are seldom above 15-20 per cent.

Finally, eosinophil leukaemia has to be kept in mind, but in this the cells are always very immature and often one-lobed, thus making differentiation easy.

The exact aetiological agent is not known. The apparent resemblance to bronchial asthma may at times be striking, and suggests a possible method of approach, *viz.*, to try and discover some anaphylactogen. Another possibility is some organismal infection for which sputum culture, separation of the various organisms present, and an attempt to test for their agglutination with the patient's serum is being tried by us. The dramatic response to arsenicals suggests a similar cause.

Prognosis

Prognosis is good, once the diagnosis is made and appropriate treatment instituted. No fatalities have so far been reported.

Treatment

Frimodt Möller (1940) reported 175 cases which had been observed for a number of years, but could suggest no specific line of treatment.

Weingarten (1943) in reporting his 81 cases described the accidental discovery of the specific effect of arsenicals, as already mentioned above. He employed neo-arsphenamine intravenously with brilliant results. He also suggested that oral use of arsenicals like stovarsol might also have a curative effect. Treu (1943) used acetylarsan, and Simeon (1943) mapharside, with success.

It is undoubtedly true, as has been amply confirmed from my personal experience that the arsenicals act as a specific by the intravenous route. Usually 6 to 8 injections of 2-3 c.c. acetylarsan or N. A. B. or mapharside or about 20 grains of soamin produce a cure.

It is interesting to record that, in our hospital we have been using soamin injections for nearly 20 years with good results in some cases, but with little success in others. One surmises that the successes were in cases suffering from this disease and not from true asthma.

In addition, stimulant expectorants with iodides are given to clear up the lung condition. Antispasmodics like tincture lobelia etheris and tincture stramonium or ephedrine are given in cases with spasm; where spasms are particularly troublesome, adrenalin .1 in 1000 in aqueous solution or in oil is of great help.

(*Continued on page 43, col. 2*)

MALARIAL NEPHRITIS

with an illustrative case report

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HISTORICAL

There is paucity of records in the literature dealing with the study regarding the pathological effects of malarial infection on kidneys. Slight albuminuria in malaria has very often been observed but one has attached no serious significance to it because presence of transient albuminuria is quite common during any fever.

One has to go back to 1891 when glomerular nephritis in quartan malaria was reported by Marchiafava and Bignami. In 1912 Clark went so far as to say that in the tropics albuminuria was an indication for searching for quartan malarial parasites, or for syphilis. Four years later Deeks (1916) opined that nephritis was one of the commonest complications of malaria. This was an outcome of his experience after working in the Panama Canal Zone. Manson-Bahr and Maybury (1927) and Giglioli (1930) reported the occurrence of nephritis as a complication of malaria caused by plasmodium malariae.

Fresh interest in this subject has been revived by Heilig (1941, 1942). He reported (1941) that in four out of six cases of acute glomerulonephritis there was a clear association with malaria, and that all these four cases responded well to quinine therapy, whereas the other two patients were discharged with laboratory evidence of permanently damaged kidneys. He established his opinion on the eitology of the nephritis to be malarial infection mainly on the response to quinine. He showed the excellent diuretic action of quinine in this condition. Heilig is of opinion that his cases were caused by *P. vivax*. Laha (1945) reported two cases of malarial nephritis. One of his cases was completely cured. The other case made a considerable improvement but he died of terminal uraemia after about two months in spite of the initial improvement. Postmortem findings of Laha's second case revealed amyloid degeneration of kidneys, liver and spleen in addition to nephritic changes (nephrotic type) in the kidneys.

In the case reported below it has been shown that the infection was of mixed type (*P. vivax* and *P. falciparum*). The next point of importance has been the failure of mepacrine therapy to strike any improvement. Rather it aggravated the lesion. There is no record regarding the effect of mepacrine in malarial nephritis.

CASE REPORT

H.C., 10 years, Hindu male child, was admitted into the hospital with the complaints of:—generalised œdema and diminished urinary output, duration 4 months. For the last 16 months he was getting occasional attacks of rigor and fever, pain in the abdomen, and transient generalised œdema. Such an attack used to last for a few days only and then subside completely. He used to take some village treatment.

On examination—The patient had universal œdema with markedly swollen penis and scrotum; was pale; and pulse and respiration rates were 120 and 28 per minute respectively; weight 3 stones and 8 pounds; blood pressure 90/64; abdominal girth 27½ inches. There was ascites, and the spleen was enlarged 3 inches below the costal margin and was firm to the feel. There was moderate amount of fluid in the right pleural cavity. Daily urinary output was 15 ounces.

Investigations—Urine: high coloured; specific gravity 1010; reaction acid; albumin present (+++); casts (hyaline, granular and epithelial), red blood cells, pus cells, amorphous phosphate and ammonium urate crystals present. Blood: total red cells 3,980,000; total white cells 13,000; polymorphonuclears 61·0 per cent., lymphocytes 32·0 per cent., large mononuclears 5·0 per cent., eosinophils 2·0 per cent., haemoglobin 7·5 g. per 100 c.c.; a fair number of B.T. schizonts and few amœboid forms present. Spleen puncture: B.T. trophozoites and M.T. crescents present. Blood urea 57·0 mg., non-protein nitrogen 45·6 mg., cholesterol 320·0 mg., and protein 6·4 gm. per 100 c.c. Stool, normal. W.R., negative. Pleural fluid: albumin 0·25 per cent., Rivalta's test negative; total cells 142 per c.mm.; polymorphonuclears 13·0 per cent. lymphocytes 87·0 per cent. Screening of the chest showed presence of fluid in right pleural space.

Progress and treatment—For one week he was given salt-free diet, limited amount of fluid, alkaline diuretic mixture 6 drams thrice daily. After a week's treatment there was no improvement at all. His urinary output and weight remained the same. Urine: specific gravity 1015; reaction acid; albumin present (+++); casts (hyaline, granular and epithelial), red blood cells, pus cells and ammonium urate crystals present. Blood urea 57·0 mg., non-protein mitrogen 45·6 mg. per 100 c.c. Then he was given 10 tablets of mepacrine within 4 days. But the patient's condition became worse. Oedema of face and legs increased. Weight became 3 stones and 9 pounds; abdominal girth increased to 28 inches, and daily urinary output became 12 ounces. Urine: specific gravity 1018; reaction acid, alubumin present (++++); casts (hyaline, granular and epithelial), red cells (in large number) and pus cells present. Blood showed no parasites. Then he was treated for one week with quinine by oral as well as intravenous routes (3, 4 and 5 grains of quinine bihydrochloride injected on three consecutive days and 15 grains of quinine sulph. by mouth every day). After a week's treatment the patient showed definite improvement. Oedema became much less and it was particularly evident on the penis and the scrotum which were massively œdematous before quinine was started. Weight became 3 stones and 4 pounds, abdominal girth went down to 26 inches, daily urinary output increased to 21 ounces. Urine: specific gravity 1012; reaction alkaline; albumin present (++); casts (hyaline and granular), red blood cells and pus cells present in very small number. During the next week he was treated with iron. During this period the improvement was maintained. After another

week he was again treated with quinine sulph. 12 grains a day by mouth for 7 days. The patient, after the completion of the treatment, showed marked improvement as evidenced by the following: Very slight œdema on legs, no ascites, no hydrothorax, spleen just palpable, daily urinary output 20 ounces, and weight 2 stones and 13 pounds. Urine: specific gravity 1005; reaction alkaline; albumin present (+); no casts; a few pus cells and occasional red blood cells present. Blood urea 45·0 mg., non-protein nitrogen 40·5 mg., cholesterol 400 mg. per 100 c.c. Blood: total red blood cells 3,450,000; total white cells 18,350; polymorphonuclears 60·0 per cent, lymphocytes 37·0 per cent, large mononuclears 3·0 per cent, eosinophils 1·0 per cent, haemoglobin 12·5 gm. per 100 c.c.; no malarial parasites present.

Discussion

The patient was suffering from glomerulotubular nephritis as evidenced by the urinalysis. The etiology of nephritis was malarial infection as corroborated by the demonstration of parasites in the peripheral blood as well as in the spleen puncture material. The parasites responsible were both *P. vivax* and *P. falciparum*. Heilig's opinion that in such cases *P. vivax* alone was the infecting parasite seems called to question. One would in this connection quote the editorial comment of *Indian M. Gaz.* (1942) :—'Professor Heilig believes that *P. vivax* was the responsible parasite in his cases, but as in most malarious countries mixed infections are the rule this conclusion must be examined more carefully'. Absence of any response to the routine diuretics but dramatically to quinine in such cases was shown by Heilig (1941, 1942) and Laha (1945). This was confirmed in the present case. In spite of the marked clinical improvement albuminuria did not clear off completely which meant that the damage of the kidneys was permanent. Mepacrine therapy failed to produce any improvement. As a matter of fact the patient's condition worsened after mepacrine administration as demonstrated by clinical and laboratory examinations. Failure of mepacrine therapy may throw some light on the pharmacological aspect of quinine in such cases. One could say that quinine does not act by destroying the parasites and thereby checking the inflammatory process. Because, if it did so then the patient should have responded to mepacrine as well. But this is a purely negative conception based upon the absence of any improvement to mepacrine therapy .

The persistence of slight œdema of legs could be explained by the persistence of albuminuria. An attempt was made to treat the patient with high protein diet but it could not be possible as he was a rigid vegetarian. The explanation regarding the increase of blood cholesterol in spite of the clinical improvement remains obscure.

Summary

A case of malarial nephritis has been described with a review of literature. Trial to mepacrine was a failure.

(*Continued on page 43*)

CLIMATE AND TUBERCULOSIS

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L. S. T. Burrel while discussing the subject of climate under Pulmonary Tuberculosis wrote the following in the Medical Annual of 1936:—

'Evans believes that climate is of secondary importance in the treatment of tuberculosis, although it used to be regarded, and still is by most of the general public, as one of the essential factors. Now it is becoming more and more recognised that rest is the essence of treatment, that provided the patient has his rest and exercise regulated by a physician of experience, the actual site of sanatorium or the climate in which he is being treated is of minor importance. He states that the treatment in unfavourable climates near the large Eastern centres of population in America can and is being successfully carried out.

'It is, however, a matter of the first importance to make the patient as happy as possible, or at least to try and remove all unnecessary restrictions which make life irksome for him, and so the psychological effect of the climate should be considered. If a patient wants to go to a certain place and has confidence that he will improve there, it is usually wise to send him, and similarly it is a mistake to send him to a place that he dislikes. For example, a patient who is pining to go to Switzerland will very likely improve rapidly if sent there, but one who dislikes the altitudes and has no confidence that crisp dry air is beneficial is better treated elsewhere. For certain advanced and very acute cases the altitudes are actually harmful, and it often happens that patients arriving at such places as Davos or Arosa have to be sent to a lower altitude. The value of the high Alps is partly due to the reduced pressure of oxygen and partly to the excess of ultra-violet light. These conditions produce a rise in serum calcium and stimulate the blood forming tissues.'

Gauvain (1930) thinks that sun treatment is not so important as alterations of heat, cold, light and shade. A change from heat wave to a week or so of dull or wet weather is beneficial for tuberculosis patients; he therefore, regards the English climate as good.

Young (1934) quotes Ellsworth Huntington:—'The climate of England comes nearer to the ideal than almost any other place'. He too stresses the importance of the variability.

The great variation in the death rate from tuberculosis in different countries in Europe suggests that climate can play but a small part. In 1926 it was as follows per 10,000 of the population (*Tubercle*, 1931).

Hungary	247	Switzerland	145
France	209	Germany	97
Spain	151	England & Wales	94
Italy	154	Holland	87

And yet people will leave England and Holland, flock to Switzerland or one of the Southern countries.

Need for Discrimination

The perusal of the above authoritative statements would make one believe that climate is of no importance

in the treatment of tuberculosis. Even then we cannot disregard the fact that certain tubercular patients show marvellous improvement and gradually progress towards recovery, when sent to a properly selected *climatic sanatorium.* I purposely mention climatic sanatorium, because in such an institution the patient is benefited not only by the climate of the locality but also by rest, open air life, good food, graduated exercise under supervision of an expert doctor and the strict routine of the sanatorium life. The mistake is often made by sending patients in an advanced stage of tuberculosis for change of climate under supervision of his relatives. The result in most of these cases is far from satisfactory. It has to be impressed on the lay public as well as on the general practitioners that the change of climate alone cannot cure tuberculosis. It may help the recovery of the patient, provided the other cardinal factors for the cure of tuberculosis like rest, good food and adequate medical help and nursing facilities are available.

Factors Concerned in Change of Climate

Very often a narrow view is taken regarding change of climate, as if, the only difference that one has to reckon with is the pure atmosphere. When a patient goes from one place to another the following changes take place in his environments:—

(1) The *air* he breathes is different. The difference may be (*a*) in its temperature, (*b*) in its relative humidity, (*c*) in its state of purity *i.e.,* presence or absence of smoke, dust particles, bacteria, fungi etc. floating in the air which have been collectively named as climatic allergens by Storm Van Leewuen, (*d*) in the velocity of the air, (*e*) in its composition *e.g.,* presence of ozone, iodine near sea side, (*f*) in its state of density and pressure *e.g.,* air in mountains is rarefied and its pressure gradually diminishes the higher we ascend.

(2) The *water* that he drinks may have different properties according to the state of its purity and amount of dissolved substances, which depends on the constituents of the soil. Thus the water of a certain place may be rich or poor in calcium, magnesium or iron or sulphates, chlorides, carbonates etc. In certain hill stations the water may contain much suspended impurities or dissolved organic substances derived from decomposing vegetable matter and thus give rise to hill diarrhœa. In other places where the water contains iron or excess of calcium it may have a constipating effect. As certain persons are habitually constipated while others have a tendency to looseness, so the properties of the water have to be taken into consideration in sending a patient for change of climate.

(3) The *food materials* available in a locality are also responsible for affecting the health of a patient. It is well known that the mineral content of vegetables vary with the chemical composition of the soil. Besides, in a place with a plenty of supply of cheap but good food materials like milk, butter, eggs, fish, fresh vegetables and fruits, the patient has a choice of a variety of foodstuffs and can avoid monotony in diet. It is needless to mention that adequate nourishing diet suited to the individual taste and digestive capacity of the patient is very important in arresting the progress of tubercular diseases.

(4) The quality of *sun-light* that the patient enjoys may be also quite different. For instance, it is a well known fact that mountainous countries receive more intense solar radiation than places situated in the plains. Smoke, mist and dust particles absorb much of the ultra-violet rays of the sun. Naturally, the sunlight in the high altitudes, where the atmosphere is pure, is richer in ultra-violet rays than that in the plains. The ultra-violet rays have strong bactericidal power and they destroy most of the germs that may be floating in the atmosphere. Hence secondary infection of open tuberculous lesions is less likely to happen in the hills than in the plains. Exposure of the body to the direct sun's rays *i.e.* heliotherapy, in certain tubercular affections *e.g.,* of bones, joints, glands, peritoneum etc. can be better carried out in the mountains than in the plains, firstly because the circulating air in the mountains being cooler than that in the plains, the patient does not feel exhausted on account of the heat and secondly the sunlight being richer in ultra-violet rays, exerts a more beneficial action by producing vitamin D in the skin and giving rise to increase of calcium in the blood and favouring calcification of tubercular foci.

Beneficial Factors in Climate

Many wrong notions are held regarding the beneficial factors concerned in open air treatment of tuberculosis. Too much stress has been laid in the past on the chemical composition of the air. But Prof. Leonard Hill has, however, conclusively demonstrated that the beneficial effect of open air treatment is mainly due to physical factors, like temperature, humidity and velocity of the air. The sense of coolness of the body surface produced by circulating air stimulates the metabolic activity of the whole organism and maintains the tone of the nervous system, specially of the heat regulating centre of the brain.

Increased humidity of the air produces discomfort and perspiration, if the temperature be elevated above 75°F or in some cases above 80°F. Again humid cool air below 70°F is apt to produce chilling of the body surface. This will be easily borne out by the common experience that one can stand much better dry cold than moist cold. Moist heat not only produces discomfort and perspiration and leads to augmentation of fever in febrile tubercular patients but also increases the risks of secondary invasion. The bacteria present in the dust and air of the plains acquire, so to speak, a greater virulence due to their more favourable chances of growth, on account of the heat and the humidity *e.g.,* during the months of August and September *i.e.,* just after the monsoons.

In this connection it is interesting to note what Sir Leonard Rogers (1936) says regarding the incidence of tuberculosis and climate. He found that 'the incidence was highest in those districts where there was most rain. Absolute humidity which is a measure of combined humidity and temperature, is important, and when this is high the tuberculosis incidence is also high. Those districts which are protected from the

full force of the monsoons have a comparatively low tuberculosis incidence'.

From the consideration of the above facts it will be evident that the three essential factors of a good climate are (1) coolness (2) dryness (3) purity of the atmosphere (*i.e.* absence of dust, smoke, mist etc.)

How Cold Affects Tubercular Patients—Cold climate has the following effects on tubercular patients:—

(1) If they were febrile before, in spite of rest in bed, their temperature goes down very quickly and has a tendency to become normal. This means that the activity of the tubercular foci becomes less in a cold climate. Friedberger and Seidenberg (1927) have shown that symptoms of acute or chronic anaphylaxis in guineapigs were not observed, if the animals receiving the injections of foreign protein were kept in cold free air at temperatures which seldom exceeded 6°C. Though of course the biochemical processes concerned in anaphylaxis, namely, the reaction between antigen and antibody leading to formation of anaphylotoxin, are not the same as those responsible for fever in tuberculosis, still there is some similarity between the two. For according to Fishberg (1932) 'the fever is engendered mainly by the increased production of heat —the result of complex biochemical processes having their origin in the struggle of the organism with the bacilli, the body summoning its defensive forces against the toxins produced by the metabolic processes of the bacilli and decaying tissues which stimulate the heat regulating centre'. From the above considerations it is quite comprehensible how cold climate can lessen febrile reaction of tubercular patients. Of course, this does not mean that a febrile tubercular person on going to a cold climate need not take adequate rest. On the contrary rest in bed is as essential for the fight against tuberculosis in a cold climate as in a hot climate.

(2) The patients sleep better and so naturally have better physical and mental rest.

(3) Their appetite improves and so they can take more nourishment and digest better. Butter, oil, fats and preparations of cod-liver oil are better tolerated in a cold climate than in a hot climate, because on account of the cold the body requires more fuel foods.

(4) The night sweats become less and less as the general symptoms of toxaemia become less marked.

In one word in a cool climate the patient is better able to fight with his disease than in an exhausting hot climate.

Dryness and Purity of Atmosphere—Dry air (relative humidity below 40%) causes irritation of the mucous membrane of nose, throat and larynx, sleeplessness, general irritability, quickness of pulse rate and dryness of the skin. If there be prevalence of wind in a dry place, dust is blown about in the atmosphere and inhalation of such dust-laden dry air often leads to nasal or pharyngeal catarrh or tonsillitis. Chronic bronchitis is aggravated by irritation of dry air. Due to excessive dryness the mucous membrane of the nose becomes too dry to function properly, namely, to humidity and heat the inhaled air. The surface epithelium is destroyed due to dryness and presence of irritating dust particles and this is followed by bacterial and virus infections, leading to common cold. It is needless to add that in all tubercular patients with ulcerative lesions of the lungs, any form of upper respiratory catarrh is very harmful, in as much as it leads to secondary infection and aggravation of bronchopulmonary inflammatory symptoms. Excessive dryness often leads to nasal bleeding due to cracking of mucous membrane of the nose. This has a very adverse influence on phthisical patients who are mortally afraid of hæmoptysis. Another important effect on the system is produced indirectly through deficiency of C vitamin in the diet on account of vegetables and fruits losing their C vitamin by the drying effects of hot dry climate. As is well known C vitamin deficiency causes bleeding from the gums and similarly it favours injury to nasal capillaries leading to nasal bleeding. One may surmise that prolonged C and K vitamins deficiency in the diet may predispose the patients to haemoptysis.

Damp air has a soothing effect on the nervous system and tends to lessen blood circulation and encourages restful sleep. This is of advantage for tubercular patients. But excessively damp mist-laden air is however prejudicial to health. It favours respiratory catarrh and augments the expectoration of bronchitic and phthisical patients with ulcerative lesions. Damp air has a bad effect on patients suffering from sinusitis. This is a very common trouble in tubercular patients and consequently damp air tends to augment upper respiratory catarrh.

It is needless to add that smoke-laden atmosphere is very harmful for pulmonary tuberculosis patients. So from the point of view of tubercular patients pure cool air which is moderately humid (about 50 to 60 per cent relative humidity) and free from dust and smoke is favourable for the healing of lung lesions.

Wind Movements—Very strong wind is harmful for tubercular patients. In a dry place strong winds blow about dust and lead to upper respiratory infections. In a moist place strong winds cause excessive chilling of the body surface which may be too uncomfortable for the patient to lead an open air life. To what extent wind movements cause chilling has been recently investigated by the Kata-thermometer in which there are 2 bulbs filled with coloured spirit, one is dry, the other bulb which is covered with wet lisle thread cap is the wet Kata. According to Hill, still air at 89°F has a cooling power, as determined by wet Kata, to the extent of 3·3. At the same atmospheric condition a wind of 9 metres per second velocity, has a cooling power, represented by the figure 15. For tubercular patients at rest a dry Kata not less than 6 and wet Kata not less than 18 is comfortable. Moderate or gentle wind stimulates the appetite and body metabolism in general. This is one of the reasons why near the sea side where there is a constant breeze there is improvement in the health. In a mountain resort where the temperature is naturally cool, strong or even moderate wind movements produce a disagreeable effect on all persons. In such a place for the location of a sanatorium a wind protected site is therefore absolutely desirable.

There is a current belief that strong north western winds accompanying a thunderstorm, common during

summer in India, provoke haemoptysis in phthisical patients. There is no satisfactory explanation for this phenomenon. I have heard experienced phthisiologists, attached to Alpine sanatoria, declare that after a thunderstorm at night they have found several cases of haemoptysis next morning. The plausible explanation of depression of barometric pressure, favouring rupture of small aneurysmal sacs on the wall of blood vessels near a lung cavity does not seem to explain the occurrence of haemoptysis, because when a tubercular patient is sent from the plains to a hill sanatorium situated, say at an altitude of 5000 ft., he experiences much greater depression of barometric pressure than usually occurs during a thunderstorm. In nervous patients a violent thunderstorm produces mental excitement, agitation and insomnia and leads to increase in blood pressure and this combined with sudden diminution of atmospheric tension may be the cause of the rupture of the blood vessels in phthisical patients with ulcerative or cavernous lesions in the lungs. In India, where the people are much more accustomed to thunderstorms and strong gales than in Europe, such nervous excitement is seldom noticed and the experience of the doctors of Indian sanatoria and hospitals bear out that the norwester gales common during April do not have any definite direct relationship with the incidence of haemoptysis in patients. Whether the rain-bearing winds which are prevalent during monsoons *i.e.* during July and August have any influence on haemoptysis has not yet been adequately investigated in India.

Absence of wind or sultriness of the atmosphere predisposes to haemoptysis. This fact has been communicated to me by my friend Dr. A. C. Guha of S. B. Dey Sanatorium, Kurseong from his personal observations. The reason for the same is, however, not known at present.

Gordon in England had found a low tuberculosis incidence in those parts of Devonshire which were protected from rain-bearing winds. He concludes that those predisposed towards tuberculosis should seek a dry, sunny, cool place with low rainfall and little wind, and protection from the directions from which the main rain comes.

Mortality Statistics are Misleading

One cannot judge the beneficial effects of a climate from the mortality statistics of a country because of the following reasons:—

1. In the same country various types of climate are met with.

2. The general economic condition of the people, their racial susceptibility have much influence on tuberculosis death rate; for instance, it is well known that people of the Latin race succumb more easily to tuberculosis than Anglo-Saxons or Teutons. In our country, hill people, who live away from civilised society, fall easy victims to tuberculosis because they have not developed the immunity resulting from subminimal infections and as such when they are infected, they develop the so-called childhood type of the disease which usually ends fatally, unless properly treated in the early stages.

3. The flocking of large number of tuberculosis cases from all parts of the world to certain climatic resorts, situated in Switzerland and France may partially explain the high T.B. mortality in those countries. In our country also many moribund or unsuitable cases are sent up to hill sanatoria where they should not have been sent at all. The fatal termination of such cases should not be cited as an evidence of failure of good climate as a factor in arresting the disease. On the contrary, it should be brought home to every practitioner that they should use utmost discretion in selecting the type of cases to be sent to the hills, and the earlier the cases are sent, the better are the chances of arrest of disease.

Concluding Remarks

There is a growing school of physicians who believe that climate is practically of no importance in the treatment of tuberculosis and they prefer to treat all tubercular patients in their own home climate, as Burrel and others have advocated English climate as opposed to continental climatic resorts. I have discussed the subject of climate in its broadest sense and pointed out the beneficial factors of climate and its effect on tubercular patients. It is true that with the frequent use of modern collapse therapy, it is possible to arrest the progress of tubercular diseases of lungs even under adverse climatic conditions of excessive heat or humidity with sultriness of weather which one frequently comes across in the plains of India. But there are still a large number of cases in whom stabilisation of the patient cannot be achieved inspite of adequate rest and all the modern methods of treatment. In such cases a change of climate to a cool and moderately humid climate in the hills may just give the necessary stimulus to the body's defensive mechanism, so that the disease is arrested without any further trouble. Climate is thus one of the factors which facilitates the healing of tubercular diseases. Just as to tide over the critical condition of the heart, say in a case of pneumonia, a doctor may have to resort to injection of cardiac stimulants, so in cases of tuberculosis, when the fight is uneven between the invading germs and the body's defensive mechanism, a change to a suitable climatic sanatorium may just help the patient to go through the adverse months of his fight and come out successfully with complete arrest of his disease. In early cases it is possible to completely arrest the disease without resort to any of the methods of collapse therapy by rest and sanatorium regime only in a climatic resort and such a cure is much more desirable from the point of view of the patient and doctor alike.

References

Guvain—*J. State Medicine*, **38**:468, 1930.
Young, R. A.—*Med. Press and Circular*, July, 1934.
Tubercle, **13**:115, 1931.
Rogers, Sir Leonard—*Tubercle*, **18**:49, 1936.
Friedbergen, E. and Seidenberg, S.—*Klin. Wochen.*, **6**:1515, 1927.
Fishberg—Pulmonary Tuberculosis, Vol. I, 1932, p. 252.

ON THE SIGNIFICANCE OF USING DECOMPLEMENTISED SERUM IN BLOOD-MATCHING

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Blood matching is of primary importance for a blood transfusion. A wrongly matched blood may not only be the source of various alarming reactions following a transfusion, but the patient may be actually killed by such an incompatible transfusion.

In looking for the compatibility of the blood we do what is called 'direct matching'. We mix a suspension of the donor's red blood corpuscles in normal saline with a sample of blood serum obtained from the patient and see if clumping occurs or not.

The basis of this is the agglutinogen content of the red blood corpuscles and the agglutinin content of the serum, clumping occurring when the corresponding agglutinogen and its agglutinin come together.

The danger lies in declaring a non-compatible blood as suitable, on account of missing the clumping, in spite of the homologous agglutinogen and agglutinin being present in the red blood corpuscles of the donor and the serum of the recipient.

This is apt to occur if the agglutinogen-agglutinin reaction is very weak and takes a long time to develop.

Majority of the clumping or non-clumping are so obvious and clear cut to the naked eye, that one is very apt to feel so secure about his judgment, as not to use the microscope as a routine, before declaring the reaction as compatible. Herein lies the danger of the very weak agglutination.

Hans Sachs (1942) of the Trinity College, Dublin, has drawn attention to the presence of some factor or factors in fresh serum which inhibits antigen-antibody reaction. Labile serum proteins present in fresh sera are held responsible for this inhibitory role. They are said to be stabilised by heating at 55°C for half an hour and making them inert and thus removing their inhibitory action.

In matching of blood the serum of the patient used is practically always a freshly obtained one. So, the possibility of the labile proteins inhibiting the agglutination reaction is to be kept in mind. To get rid of this inhibitory action, if possible, should be the aim of all doing the blood matching.

TABLE SHOWING RESULTS OF EXPERIMENTS

Blood Group of the person whose serum is tested.	*Agglutinin content of serum.*	*Tested with r.b.c. of Group*	*Serum dilutions*									
			Undil.	1:2	1:4	1:8	1:16	1:32	1:64	1:128	1:256	
A	Beta	B	+	(+)	W	−	−	−	−	−	−	Unheated
			V	V	+	W	−	−	−	−	−	Heated
O	Alpha & Beta	B	+	+	+	(+)	−	−	−	−	−	Unheated
			V	++	++	+	(+)	−	−	−	−	Heated
B	Alpha	A	++	+	+	(+)	−	−	−	−	−	Unheated
			V	++	+	+	(+)	−	−	−	−	Heated
O	Alpha & Beta	B	++	++	+	+	(+)	−	−	−	−	Unheated
			C	V	V	++	+	W	−	−	−	Heated
B	Alpha	A	V	++	+	+	(+)	−	−	−	−	Unheated
			C	V	V	+	+	−	−	−	−	Heated
O	Alpha & Beta	A	C	V	+	+	W	W	−	−	−	Unheated
			C	C	V	+	+	(+)	−	−	−	Heated
O	Alpha & Beta	B	C	V	V	++	+	(+)	−	−	−	Unheated
			C	C	C	V	+	+	W	−	−	Heated

C (complete) = Clumps of cells in clear surrounding fluid visible to the naked eye.

V (visual) = A somewhat weaker reaction with clumps distinctly visible to the naked eye, although the surrounding fluid is not clear.

++ = Very big clumps under the microscope. + = Not quite such big clumps.

(+) = Less than + , clumps of 8-12 cells.

W (weak) = A definite but weak reaction in which there is a uniform distribution of very small clumps of about 4-6 cells.

− = No clumping *i.e.*, discrete r.b.c. under the microscope.

N.B.—System of scoring is on the lines advocated by Taylor *et al. J. Path. & Bact.*, January, 1942.

Experimental

To what extent the heating of fresh serum can intensify the reaction, comparative observations were made between the agglutinations given by fresh unheated serum with the reactions obtained with same serum heated.

A suspension of a red blood corpuscle containing the corresponding agglutinogen was made for each of the sera tested. So far 52 cases have been investigated. The source of the serum tested was confined to those cases where the freshness of the sera was guaranteed. Only the samples of blood collected within 24 hours were used.

To note the differences in the intensity of agglutination and in order to be able to make smaller differences obvious, it was necessary to obtain the serum in different concentrations. For this a series of increasing dilutions was obtained separately for this heated and the unheated serum. Each of these dilutions was tested with the same suspension of red blood corpuscles. Test tube technique was adopted.

It was noted that barring a few cases *i.e.* only 4 out of 52, a distinct difference was observed between the agglutination given by the fresh heated serum in comparison with the same when unheated.

The differences observed showed an increased intensity of agglutination in the fresh heated serum in contrast to the same when unheated. This has been manifested not only in the sera with low titre of its agglutinin, but also in those possessing a greater concentration of the same.

In some of the cases, 6 out of 52, it was found that the clumping given by the fresh unheated sera was so weak that clumping could only be detected when seen under the microscope, even with undiluted sera or the next dilution *i.e.* 1 in 2. These were the cases with low agglutinin titre up to 8.

But a marked change occurred when the suspension of the red blood corpuscles was tested with the same fresh serum, but this time after heating at 55°C for half an hour, what was only microscopical clumping with the unheated serum, became strong enough to be obvious to the naked eye when heated serum is used.

In the cases of sera with greater concentration of agglutinins (titre 16-32 or beyond), the intensity of agglutination was strong enough in the undiluted fresh unheated serum to be obvious on naked-eye examination. The effect of heating in intensifying the agglutination, however, was also manifested in these cases, specially towards the higher dilutions.

Haemolysis Occurring in Certain Cases

In a certain number of cases (9 out of 52) another phenomenon was observed in addition. This was hæmolysis or laking of the red blood corpuscles. It was interesting to note that this hæmolysis occurred only with the fresh unheated serum. No such hæmolysis was observed when the same serum was used after heating at 55°C for half an hour. This hæmolysis of the red blood corpuscles with the fresh unheated serum was confined either to the undiluted or at the most the dilution of 1 in 2, the concentration of serum usually used for matching.

Unless one keeps this fact in view, the hæmolysis can create confusion in the mind of the worker. He will find it difficult to say if the red blood corpuscles and the serum are compatible or not, as he neither sees red blood corpuscles nor the clumps under the microscope. The absence of clumps under the circumstances may lead one to a wrong conclusion of compatibility, unless he is able to appreciate not only the absence of clumps, but absence of discrete red blood corpuscles as well. This is naturally of great practical significance in actual blood matching and heating of serum at 55°C for half an hour which removes this factor is a definite improvement.

Greval *et al* (1943) mentions of two iso-hæmolysins, *i.e.* anti-bodies in the serum that will bring about hæmolysis of the particular group red blood corpuscles one *b* in a person belonging to group 'O' and another *a* also in an 'O' group person. He mentions of these iso-hæmolysins being inactivated by heat.

Whether the hæmolysis occurring with fresh unheated serum in my cases were due to such iso-hæmolysins in the sera as described by Greval (*loc cit.*) or due to some other factor, I am not yet in a position to say. The cases showing hæmolysis included sera not only from persons belonging to group 'O' but also from persons of 'A' and 'B' groups.

Salt Concentration in Blood Matching

The salts (electrolytes) are necessary for an agglutination reaction between the antigen and the antibody, in our case the agglutinogen and the agglutinin. The precise way as to how the electrolytes work has not yet been fully elucidated. It is said that it acts by reducing the electrical potential between the cells, thus minimising the mutually repellent influence of the similar electrical changes carried by the cells.

Sachs (*loc. cit.*) has suggested using of higher concentration of salts in preparing the red blood corpuscles suspension (instead of the usual normal saline *i.e.*, 0·85 per cent NaCl) to intensify the agglutination. Use of 2-3 per cent NaCl solution has been advocated.

A few of my cases were put up with red blood corpuscles suspended in 2 per cent NaCl solution as well as the normal saline and both such suspensions were tested against fresh heated and unheated serum. The intensities of agglutination showed that increase in the salt concentration to 2 per cent can further intensify the reaction over and above that obtained by heating the serum at 55°C for half an hour.

Conclusions

1. In doing direct matching for selection of compatible donors, it is an advantage to heat the serum at 55°C for half an hour, as this intensifies the agglutination by stabilising the labile proteins present in fresh serum which inhibit the reaction.

2. The importance of this inhibitory factor in fresh serum lies in that its suppressing effect may vitiate agglutination reaction during direct matching between incompatible serum and red blood corpuscles. This is particularly liable to happen with weak sera.

(*Continued at foot of col. 2, page 57*)

SPECIAL ARTICLE

HEALTH SERVICES OF THE SOVIET UNION*

R. S. SAXTON, MAJOR, R.A.M.C.

INTRODUCTION

The Social revolution in Russia made possible an enormous economic development, which in turn made possible the most comprehensive social services in the world. Without the economic foundation these social services could not have been achieved, and without the social services the tempo of economic development could not have been maintained.

PRINCIPLES

Human beings are recognised as the most important assets of the U.S.S.R., and to maintain them in the best possible health is recognised as a matter of first importance and as a national responsibility.

BASIS

There are many factors which contribute to and form a firm basis for the Health Services of the U.S.S.R. Some of the more important ones are as follows:—

(1) *Trained personnel*—Instead of the previous total of 14,000 doctors in the whole country, about twice that number now qualify annually, and the total in the country is of the order of 2,00,000. The total number of doctors in relation to the population has in fact altered in the course of 30 years from a condition similar to that in India to a condition similar to that prevailing in England.

(2) *Premises*—The increase in medical personnel has been accompanied by a gerat increase in hospitals and in the development of many new institutions: in particular polyclinics and rural medical centres, and in the turning over to use as sanatoria and rest homes, of many royal palaces etc.

(3) *Equipment*—Instead of having to import all but the simplest drugs and apparatus, now there is practically nothing from x-ray apparatus to sulpha drugs that is not made in the U.S.S.R. These products are supplied to individuals and organisations by some 10,000 state pharmacies; and drugs only at a further 20,000 retail shops in the country-side. There is no patent medicine trade.

(4) *Food*—Russia used to be the 'granary of Europe', but after the first 5-year plan less and less grain had to be exported, as indigenous industries supplied many of the products previously bought abroad. At the same time greatly increased production was obtained by collective farming and greater variety in food production was introduced. Thus the diet of the people has been enriched in qualitiy and quantity to the great benefit of their nutrition.

(5) *Social security*—The certainty that undergoing treatment will not result in disastrous financial loss and unemployment, and to know that no question of cost will prevent the best treatment being given, remove many of the anxieties which may prevent people from seeking medical advice in good time, and in persevering to the completion of all treatment and convalescence that may be required.

(6) *Leisure*—Two to four weeks holiday per annum on full pay was the established rule, and the shortest working day in the world prevailed, in the U.S.S.R. before the war.

(7) *Education*—The abolition of illiteracy, the emancipation of women, the teaching of ideas of cleanliness, fresh air, exercise, proper diet, disease prevention: all these accompanied the unparalleled extension of general education to 34,000,000 pupils.

THE SCOPE OF THE HEALTH SERVICES

(1) From the earliest sign of disease to the end of convalescence a complete service is available to the whole population irrespective of financial considerations.

(2) Public health preventive medicine, and curative medicine are closely linked and are often undertaken by the same institution.

(3) Positive improvements in health are facilitated by improved diet in the large-scale public catering for workers, through energetic housing programs, through the provision of proper bathing facilities, the encouragement of sport, etc.

MOTHER AND CHILD

All expectant mothers are encouraged to attend antenatal clinics for general supervision and advice, and in many towns there are 'museums of mother and child' where they may see model layettes, simple toys, cradles, etc., and get advice on feeding, hygiene, or even on legal and financial matters relating to motherhood.

Pregnancy leave on full pay is 5 weeks before birth till 6 weeks after birth, and longer if medically advised. If the mother chooses to return to work, the factory farm or district will provide a creche to care for the child in working hours. 1,800,000 babies are regularly cared for by trained staff in these institutions, and some 10,000,000 at harvest time. Mothers get time off from work to feed their babies. In the best creches, they wash and put on a clean gown for the purpose. The mother can also receive, at small cost, a suitable meal at the creche.

SCHOOL MEDICAL SERVICES

Every school has a doctor in part-time attendance. His duty is not only to attend the children when sick, but he has a number of other responsibilities.

(1) He advises the school on matters of hygeine, and usually he has to assist him in the execution of his suggestions one pupil elected from each class who is responsible for seeing that the school rooms are well ventilated, the ablutions are satisfactory, that habits liable to spread infections are discouraged, etc.

(2) He usually gives lectures on various medical subjects, including first-aid, and he will answer either

* Read at a meeting of Calcutta Branch of the I.M.A. on September 20, 1945.

privately (if so requested), or publicly in his lectures (if of general interest and importance) questions the pupils may put to him in writing in his 'question box'.

(3) He carries out the annual health inspection which is compulsory for all children in the spring, when cases are selected for sanatoria or rest home as may be necessary. In addition schools usually organise holiday camps where pupils may enjoy a healthy outdoor life for a part of their summer holiday.

General Public Services

Medical attention is usually provided for the public through ambulatoria*, polyclinics† and hospitals in residential areas or in the places of work.

Ambulatoria do the work of the general practitioner and polyclinics that of the 'out-patients' of a hospital as we know it. They contain all the usual special departments, and have laboratory, x-ray, physio-therapy and other special facilities. They send out doctors and nurses on domiciliary visits. In the country the corresponding institution is the Rural Medical Centre which can hold a few in-patients at a time, being usually distant from a hospital.

Hospitals are closely linked with polyclinics. Big factories often have their own polyclinic, and if not their own hospital, have a number of beds in nearby hospitals reserved for the use of their patients. Factories also may have their own rest homes, sanatoria and maternity homes, all run by the Trades Union. Including maternity beds, there are nearly 1,000,000 hospital beds in the U.S.S.R. The level of treatment in the modern hospitals is up to the best European standards. Examples in the field of surgery are the great advances in the technique of corneal grafting made by Prof. Filatov in Odessa, and some of Prof. Yudin's cases we saw in Moscow in whom a subcutaneous artificial oesophagus had been constructed. The medical staff of hospitals and polyclinics are all salaried, and their salaries varied in 1936 from 600 to 1000 rubles a month, for a 6-hour working day. They were permitted to take on other part-time appointments, and many did so. Nurses lived in their own homes outside the hospitals, and worked regular and reasonable hours.

Public Health

Coupled with the administration of the medical services or the individual there has been a big development in Public Health.

A clean piped water supply and water-borne sewage systems have been installed in all towns and many country places. To this may be largely attributed the fact that cholera once a scourge, has now been completely eliminated.

Compulsory vaccination of children has similarly eliminated small-pox in that section of the population. Compulsory diphtheria inoculation has greatly reduced the incidence of diphtheria, and it has completely vanished from certain localities. Inoculation with T.A.B., at one time pursued with great vigour, while proper sewage disposal was being provided, reduced the incidence of enteric diseases very considerably.

Anti-malaria stations combine attention to diagnosis and treatment with attacks on the breeding grounds of mosquitoes, including spraying from the air. Malariologists accompanied evacuees going east into parts of the U.S.S.R. where malaria is endemic, and undertook immediate treatment of any case, so reducing the spread of the disease. The drug used is Akrakhine*, a Soviet preparation.

Trachoma has also been dealt with from a public health point of view. Trachoma posts, dispensaries, and research institutes have co-ordinated prevention, treatment and research. The result has been that the spread of the disease, even under war conditions, has been prevented; and that the incidence of the disease and of blindness resulting from it, has been much reduced.

The general results in improved public health can perhaps be best appreciated by considering the figures of infant mortality. The figure had been reduced from about 250 per 1000 in Tzarist days to about 90 per 1000 in the late 1930s. It should be noted that these figures include large numbers of people living in remote and previously very backward parts of Asia. The figure in England at the time was about half this number (though probably about double this number for the whole Empire), but the rate of improvement in the two countries indicated that, but for the war, the U.S.S.R. would have caught up with England before 1950. Figures for the incidence of T.B., and of T.B. and general mortality, were in similar proportion to those in England. One interesting point in the comparison of the figures for T.B. incidence and mortality was the relatively steady improvement in the U.S.S.R. before the war. Comparing two ports, for instance, Bristol and Leningrad, it can be shown that during the period 1929-1933 a deterioration took place in Bristol whereas steady improvement continued in Leningrad. Bristol was, of course, adversely affected by the economic slump, but slumps are unknown in the U.S.S.R., and this economic difference is reflected in the changes in T.B. incidence and mortality.

Miscellaneous

The enormous variety of types of organisation within the Health Services does not permit of a comprehensive account in one lecture. A few further matters of interest may be briefly mentioned.

(1) *Moscow accident service*—Hospitals are designated in each area to receive road accidents and other emergency cases. A team of doctor and abmulance staff is always standing by. They have to be out of the hospital on their way to the accident within 3 minutes of receiving the call. If not, an enquiry is held.

(2) *Railway station nurseries*—At important railway junctions where waits may be protracted,

* Ambulatorium—10,000 patients, 14 doctors, dentists, Lab., x-ray.
† Polyclinic—100,000 patients, 200 doctors. All specialities.

* I. M. Injection, painless. No tinnitus. More slowly excreted than quinine.

nurseries are provided where parents may leave their children in competent hands all day. The children will receive food and attention at small cost and will have plenty of toys and company. Meanwhile the parents can go out and see the town, etc. The nurses are selected partly on account of their linguistic capabilities, so as to be able to deal with children speaking any of the main languages of the U.S.S.R.

(3) *Prostitution*—This profession has practically vanished: principally because there is an opportunity for honest work for everyone. To deal with ex-prostitutes prophylactoria were provided in all large towns, and later it was possible to reduce their number to three only in the whole of the U.S.S.R.

These prophylactoria combine training for some useful occupation with treatment for V.D. if present. The women are paid while at the institution, and are found jobs in factories when trained. Some find work in factories difficult, and these are permitted to continue living and working at the prophylactorium at a small salary.

(4) *Venereal disease*—Once diagnosed, treatment of V. D. is compulsory until cure is pronounced. Patients knowing they have the disease, and transmitting it, are liable to severe penalties. This attitude combined with the abolition of prostitution and the high level of general culture achieved, have reduced V.D. to a low level. Syphilis had in fact entirely disappeared from parts of the U.S.S.R. before the German invasion reintroduced it.

(5) *Night sanatoria*—These are institutions where people who are temporarily unfit for home life, and require some health supervision, can spend a few weeks while continuing part-time or full-time work. Examples are: cases of open T.B. liable to infect their families, or skin disease such as psoriasis. Any necessary treatment can be given in the evening, and the patient is obliged to spend a quiet evening, take some suitable food, and go to bed in good time.

(6) *Flying squads*—These are medical units comprising consultants and specialists, with the necessary assistants and apparatus, who fly on a regular schedule to distant rural centres to advise and treat patients selected for their attention by the country practitioners in the intervening period.

(7) *Research*—In each field of research there is a Central Research Institute which plans the research work in that particular field for all research institutes in the country. There are over 100 large research institutes covering medical subjects. Publications dealing with their work are printed in 45 monthly journals. There are two general medical journals, and the Commissariat of Health publishes its own daily paper.

(8) *Medical education*—In the 82 higher medical schools the course is now being increased from 5 to 6 years. After the first 4 years a partial specialisation takes place according to the type of work the student prefers. The three types of work are:—curative-medical, sanitary-hygienic, and pediatric. Of the 25,000 to 30,000 annual intake of students, about 75% are women.

Education, however, does not end with qualification: for a refresher course is compulsory every 3 years. There are also associations of doctors in the various specialities who arrange lectures, demonstrations, etc. in all large centres.

War Developments

The public service already existing made a transition to a War service relatively simple except that so many more doctors were rapidly required and so much more surgery had to be done. However all difficulties were overcome as evidenced by the fact that over 7% of the wounded returned to military duties.

Some points of interest are:—

(1) The number of medical students was greatly increased, and 100,000 doctors were trained in 3 years. Considerable numbers of specialists with a certain knowledge of surgery were given a course in general surgery, pending the training of a sufficient number of newly qualified surgeons.

(2) Specialist hospitals were developed for all kinds of surgical conditions, and great successes were achieved in these hospitals. For instance: a doctor who had lost both arms, one above and one below the elbow, was enabled to look after himself, to type, and to act as Public Health Inspector.

(3) Advances in blood transfusion. Much pioneer work in transfusion had already been accomplished in the U.S.S.R. before the war: for instance, the use of cadaver blood whose collection we observed in Moscow.

During the war, as in other allied countries, whole blood and dried plasma were used on a mass scale, and air supplies were available to advanced forces and to guerrilla units.

A new technique which has been tried with encouraging results, has been arterial transfusion of patients whose condition indicates that a transfusion into a vein would be unlikely to be effective. Such patients are in coma, have an imperceptible pulse, and have practically stopped breathing. 200 c.c. to 300 c.c. of blood at 160 to 200 mm. of mercury pressure is injected into the brachial artery. This closes the aortic valves and forces blood through the coronary arteries, restoring the heart beat sufficiently for a venous transfusion to restore the circulation. This treatment has to be combined with vigorous artificial respiration using an intratracheal tube and a bellows.

Conclusion

Organisationally the Soviet Health Services are the best in the world. They rest on the firmest foundation in the world. They suffer from the backwardness of the past, so that they have not, in comparison with some countries, the same proportion of older, more experienced trained men and research workers. This is a matter which will be put right with the passage of time. They suffer still from the past very bad Public Health and terrible poverty. This has left its mark in T.B., infant mortality, etc., but there can be no doubt that a decade or so of peace will enable the U.S.S.R. to lead the world in these respects too.

ADDRESS

PROGRESS OF SURGERY IN THE PROVINCE OF MADRAS*

T. S. SHASTRY, LT.-COL., I.M.S.

As a little boy I happened to see a Hospital Assistant pass a metallic catheter in a struggling adult in my neighbour's house and draw some bloody urine. It was in Kottajatam in the Nellore district. This simply horrified me and for many years haunted me.

As a school-boy I used to attend the post-mortem work of the Local Fund Hospital Assistant in Giddalore, Kurnool District, during my summer vacation. This led me to think on the beauties of the structure and functions of the internal organs of the human body.

My father was a patient suffering from a chronic disease and often used to ask me to take up the study of Medicine.

Dr. Pattabhi Seetharamiah was the first Andhra M.B. and C.M. (1907)—a pionner for us, Andhras, and furnished a stimulating example.

I saw terrible sight one forenoon in May 1908 while travelling in a bullock cart on the Bunder-Bezwada road. A boy of 10 years fell vertically down on the road in front of me from the top of the tree about 50 feet high. His right arm snapped and two broken pieces shot out.

All these interested me greatly and quickened my desire to join the Medical College. I joined it in July, 1908.

In those times the state of surgery was thus:—

Abscesses, carbuncles, superficial tumours, amputations, piles, fissures, fractures, hydroceles, urethral strictures and hernias—whoever did these operations became famous as a great surgeon. Hernia was a serious operation! Removal of elephantoid scrotum was a big undertaking! Removal of cataractous lens was a wonder! Forceps delivery and completing an abortion formed the obstetrical surgery of those days! D & C was the stock-in-trade in gynaecology. Chloroform was the only anæsthetic and was usually administered by compounders. Most of the surgical work was confined to district hospitals, and that was the monopoly of the I.M.S. officers.

Dr. Nedungadi was the first Indian to be appointed as a Surgeon in the Madras General Hospital in 1916. That was a land mark indeed! Dr. Rangachari was the first Indian Surgeon who performed really first class surgery. No part of the body escaped his knife. His work was good both in quality and quantity.

Among independent practitioners, none had a nursing home with theatre, staff and equipment. Dr. T. M. Nair did some E.N.T. operations but he was not noted as much of a surgeon. Dr. Varadapra Naidu did some carbuncles, having worked with Major Smith who resigned from the I.M.S. Dr. Naidu was much in demand in the districts. Generally, people from all parts of the Province resorted to the General Hospital, Madras. Surgery by independent practitioners was an uncommon phenomenon in those days. Thus arose the general notion that no Indian was competent to do decent surgery and that surgery was really a monopoly of the British I.M.S. officer.

In 1912, one evening in May, I met at Bhimadole (West Godavari District) the huge, uneducated son of an old-time zemindar who was a famous hunter. He openly told me not to attempt to do surgery as no Indian was ever competent temperamentally to do good surgery, and he went on praising Major Niblock of the Madras General Hospital for his skill for operating an abscess on his leg! This stung me to the quick, and I determined to break this tradition. So, when I got the chance, being surgically inclined by nature, I devoted myself to surgical work. I have ample reason to be gratified with my choice.

The first Great War was a windfall indeed to us Indians who were keen on doing high class surgery. Nearly all the I.M.S. officers were then pulled away to war-duty. Some of the assistant surgeons had to be given charge of district hospitals and teaching jobs in medical colleges and schools. This opportunity proved their intellectual calibre, professional skill and efficiency of hospital management. Many of them proved to be good and great surgeons. Drs. Chandrasekhara Mudaliar, Ganpat Rao, Madhava Rao, Halge, Krishniah, Padmanabha Sarma, V. Krishna Murthy, Trasi, R. Ganapathy Iyer, Nedungadi, Ranga Chari, Lakshmanswami Mudaliar (now Sir) created the surgical era in 1915.

Of all these, the most out-standing surgeon was undoubtedly the late Dr. S. Ranga Chari who practically lived in his Rolls Royce—an 'ever ready' surgeon, noted for his popularity, quickness, studied reserve, and a spirit of universal sympathy and service—all this success came to him without any foreign traning thus showing what a mere M.B. & C.M., could do. In any other country he would have surely been honoured by his Alma Mater with the Honorary Degree of M.S. or D.Sc. But the University of Madras had no imagination, nor a sense of magnanimity or propriety to honour one of its own brilliant alumni. The grateful public, however, installed a full-sized statue of Dr. Ranga Chari appropriately at the very entrance to the General Hospital.

Among the independent practitioners in Madras, Dr. E. V. Srinivasan led the way in eye surgery, while Dr. T. S. S. Rajan became quite an institution in Trinchinopoly. Dr. Ramasubramaniam came into fame in Madura quite early in his career. Then came the honorary system. The honorary surgeons made quite a good place for themselves in some hospitals.

Now-a-days surgical skill of high order is available in many towns. Many surgeons have equipped themselves for advanced surgery by training in foreign countries. Nobody now dreams of preferring a British to an Indian surgeon unless it be Dr. Somervell of Himalayan fame—but that is not because he is British but because he is a great surgeon, and a humanitarian like the late Rev. C. F. Andrews of blessed memory—in fact he is a citizen of the World.

Thus the old fiction that high class surgery is the monopoly of the British race has been exploded by

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*Address delivered at the Surgical Section of the South India Provincial Medical Conference, Trichinopoly, Oct., 1945.

Rangachari and others. Today many Europeans—both civil and military, go to Col. Pandalai, Dr. Mangesha Rao and others.

Starting of nursing homes was the next development. I remember Dr. Lakshmipathy's Nursing Home in Madras in 1910. But it was only in name and soon disappeared. Dr. Rajan's was really the first nursing home started, maintained and well-equipped, and he has done good work indeed in this line. Then came Dr. Rangachari's surgical hospital in Madras. He did most of his first class operative work there, and trained some juniors who, in turn, have opened nursing homes which are all flourishing. Dr. Ramasubramaniam started his nursing home in Madura and is doing very good work. Col. Pandalai has built a palatial private hospital for surgery—this is easily the best of its kind in our presidency. Dr. Sundaravadanam followed suit in Madras. Captain Sunkavalli has a good one at Bezwada. Dr. Raju and his partner have an ambitious nursing home in Palakol, West Godavari. Dr. Subramaniam's is a good one at Karaikudi with a good record of work. Trichinopoly itself has three other nursing homes—Dr. Raghavan's, Dr. Kalamagham's and Dr. Balu's.

During the Second World War, now happily ended, many young and aspiring surgeons served in the Defence Forces in all the different sectors. They have done splendid work, acquired experience, attained high military rank and very good name. Here I must mention with sincere pleasure my own junior officers, Major V. Srinivasan and Lt. K. Parthasarthy who served on my staff when I was Commanding the 30th. Indian General Hospital in Sudan and in Egypt in 1941 and 1942. The doctors of this Province, I am glad to say, have volunteered in largest numbers, gained a lot of military and surgical experience and international contacts in the various theatres of war, and added to the reputation of the Indian medical profession; of them we are justly proud.

I hope that when these surgeons return to civil side they will be given suitable jobs in the hospitals in the metropolis and other towns. Those who cannot get such jobs ought to be encouraged to open and maintain their own surgical homes with the aid of demobilised nurses—if possible on co-operative basis, with pathological laboratory x-rays, etc.

The large quantities of surgical and medical equipment which the American and British find to be surplus when their military hospitals are closed should be secured by the Government for Government, local fund, missionary and other hospitals for the surgical use. Our medical colleges have, of course, better surgical staff than before, and I am sure that they will produce better results if given the required equipment. For obvious reasons I am not detailing the names of their staff. Perhaps the best agency for these surplus stores to be made available to surgeons is the Govt. Medical Stores which may open a Sales Dept.—I have taken this from Dr. M. V. Natesan of Madura.

The crying need today is more medical colleges. We have one at Vizag, two at Madras, one at Vellore, and one is under design for Madura. But what about the northern districts? I hope that the policy of neglect of the Andhra area will not be continued hereafter. I expect Guntur will get a medical college started in July 1946. The required staff, if there is paucity, can be provided for by employing for some time some of the retired surgeons and physicians who are keen and fit to take up this work. Meanwhile the required number of staff must be selected and sent out by the Government to the U. S. A. and trained adequately in all the subjects and employed on suitable terms in these new medical colleges.

In selecting these and other personnel and specially in dealing with the proper employment of war-returned medical and nursing personnel, the Government will be well advised to take the advice of the Indian Medical Association by asking the I.M.A. to send its representatives to the selection committees.

One warning is needed now. Enough experimentation has been done and enough mischief, injury and discontent and even frustration have resulted from the implantation of stern communalism in the matter of admissions into the medical colleges. It is time that a just policy is adopted.

One very good development is the starting and growth of the Association of Surgeons of Indian in 1938 as a result of the initiative of Col. Pandalai. It is flourishing. I hope this and other specialist' Associations —which by the way had their birth-place in Madras, (at least, most of them) agree and arrange to hold their sessions jointly with the Indian Medical Association hereafter, and thus make themselves useful to the general body of the profesion. In this connection I greatly appreciate the efforts of Dr. Jivraj N. Mehta.

Are we fully satisfied with the present state of our surgery? I believe special attention must be given to the surgery of the brain, surgery of the chest, reconstructional surgery and surgical research. Adequate surgical training is necessary. Surgical workshops for artificial limbs etc., and experimental laboratories are to be established for each teaching hospital. Vienna is no longer the Mecca or Kāshi of modern surgery, but the Mayo clinic and others of its kind will give all facilities to us in the U.S.A.

Fellow members, there is a great future and scope for surgery in our country if all the available material be properly utilised and if we serve the people with integrity, sympathy and devotion.

(*Continued from page 52*)

3. In those with high agglutinin titre, hæmolysis occurred instead of agglutination with undiluted or 1 in 2 dilution of fresh serum. No such hæmolysis but strong clumping was observed when the serum was used after heating at 55°C for half an hour.

4. Increasing the salt concentration to 2 per cent for preparing the red blood corpuscles suspension instead of using normal saline as suggested by Sachs, can further intensify the agglutination. Two per cent saline may be used for direct matching where facilities for heating of the fresh serum at 55°C for half an hour is not available, and even in conjunction with the latter.

REFERENCES

HANS SACHS—*Lancet*, **1**:473, 1942.

GREVAL, S. D. S. BHATTACHARJI, J. N., AND ROY CHOWDHRY A. B.—*Indian M. Gaz.*, **78**: 593, 1943.

JOURNAL OF THE

INDIAN MEDICAL ASSOCIATION

CALCUTTA, NOVEMBER, 1945

POSTMORTEM EXAMINATION

We offer no apology to return again to the subject of postmortem examination. Since we discussed[1] it about four years ago, one regrets to notice that the situation has not improved in any way. From the number and nature of articles published from our country, one is forced to arrive at the above conclusion.

From many a platform it has been declared that standard and quality of medical research in our country is not what it should be. There is no denying this fact and if we want to change this position we must face reality. Among a number of other reasons for this quality of research, lack of postmortem examination is undoubtedly one. From a series of figures published by Tribedi[2] it can be said that during 1930-1939, a period of ten years, postmortems were held in less than 5 per cent of the total deaths in the hospitals. These figures were taken from all teaching institutions in this country. In one hospital attached to a medical school only two postmortems were done against an average of about 2,500 annual deaths! How can teaching or scientific medicine progress under these circumstances? What is the cause of this poor record? In every teaching institution there are facilities for autopsy. There are responsible teachers and clinicians attached to or appointed in them. And it is also a fact that everywhere there are no communal organisations which want the unclaimed bodies for disposal. The cropping up of these communal organisations is unfortunate but what is their legal status in respect of unclaimed bodies? Are the teaching institutions bound by law to hand over these dead bodies, without performing a postmortem examination in order to verify the diagnosis or are the medical men in charge reluctant to go through the examination? It is surely not a common sight in our country to find the postmortem room filled up with clinicians, pathologists and students.

Tribedi (*loc. cit.*) suggested three courses to increase the number of autopsies *viz.*, (*a*) State legislation (*b*) Voluntary permit (*c*) Postmortem examination done on unclaimed bodies. In addition one may suggest the signing of a declaration by the relatives that they will not oppose a postmortem examination, if necessary, before a patient is admitted to any hospital. The idea of voluntary permits appeals to us as being more reasonable than others. For this education of the public is essential. This can only be done by medical men who are at the helm of the profession both in private practice and in the institutions. The question of an operation on the dead in our country is always opposed on delicate sentimental ground. This can be dispelled by propaganda, tact and friendliness. The relation between a patient and a clinician, whether a surgeon, obstetrician or a physician should be more cordial. It cannot be denied that we seldom try to develop this relation in our country in contrast to what one sees in the West. It is amazing how some leaders of lay public are ignorant and sentimental about this question of autopsies. To start with, these men are to be won over. State legislation and others can help the matter in later stages.

As members of the profession, we can hardly put all the blame on the public. There seems to be a camouflaged tendency to avoid autopsies by many of us. One of the reasons for this as pointed out by an editor is[3] 'If the medical teacher in India has a weakness, it is dogmatism. He has inherited it from his predecessors; it is encouraged throughout his life by the childlike and unquestioning faith that many students place in their teacher; and it is fostered by the comparative isolation from colleagues of equal or superior mental calibre. Nothing encourages this attitude in a teacher than the thought that, as he is a king pin in his own little circle, he can never prove to be wrong, and nothing could be more salutary for it than the occassional cold douche of a postmortem finding that directly contradicts his clinical diagnosis'. And we think he should take such an education with all the grace in front of his colleagues and students.

The testamentary instructions[4] of Lord Dawson of Penn throws a new light on this subject. An eminent physician and one time the President of the Royal College of Physicians, he directed that, if conditions of war permitted, a postmortem examination on his own body should be made. He wrote: 'I do this because I think the public do not sufficiently realise the importance of postmortem examination being made and the advantages to knowledge and therefore to future generations which will thus accrue. We do not hesitate to have operations on our bodies when we are alive and when circumstances require it. Why, then, should we mind operations (which are done with the same care, the same gentleness, and I may add the same reverence) being done on our bodies when we are dead? Surely this is a rightful service which the dead should give to the living. The benefit of such service to the living is very great.'

[1] Editorial—*J. Indian M. A.*, **11**:49, 1941.
[2] TRIBEDI, B. P.—*Indian M. Gaz.*, **76**:546, 1941.
[3] Editorial—*Ibid.*, **76**:545, 1941.
[4] *Lancet*, **2**:292, 1945.

CURRENT MEDICAL LITERATURE

Effort Syndrome

Hill and Dewar (*Lancet*, **2**:161, 1945) give in the following lines the summary of their observations:

The observations are based on 489 cases of effort syndrome observed in Britain and the Middle East during the present war; the clinical features in 392 of these are reviewed.

At a hospital in the Middle East at which all cases of effort syndrome in the Force were centralised, these cases constituted less than 1% of the 25,000 medical and surgical cases admitted to the hospital in twenty months.

The condition is not confined to the young or to men unaccustomed to hard physical exertion, and the onset in a large proportion long antedates entry to the Service.

Serious or protracted illness in childhood, rheumatic and non-rheumatic, predisposes to the development of effort syndrome. In a high proportion of cases the condition is partly at least 'doctor-made'.

The relative frequency of various precipitating factors (physical strain, battle experiences, recent infection, domestic worry, etc.) is discussed. Many cases arise without exposure to undue physical or mental strain apparently in individuals of inadequate physique and personality.

The treatment by graduated exercises and reassurance carried out at a general hospital in the Middle East in 1941-43 is described. A follow-up investigation carried out by Medical Directorate, GHQ, MEF, showed that nine months after discharge some 80% of 254 cases traced were on full or light duty with their units.

Gastrointestinal Symptoms of Heart Disease

MacMillan and others (*Am. Heart J.*, **29**:580, 1945) write that the condition presented involves a patient who after coronary occlusion, developed heart failure, the primary symptoms of which were nausea and vomiting, and in whom the significant pathologic changes were multiple areas of myocardial fibrosis. As a result of the experiences with this and other similar cases and a review of the literature, the following conclusions are drawn;

1. When nausea and vomiting are dominant symptoms in a case of heart failure, one should consider as possible factors not only drugs, congestion of the abdominal viscera, and disorders of the blood metabolites (such as occur in uraemia), but should also entertain the possibility that progressive myocardial disease may be the cause of the symptoms.

2. The mechanism of the nausea and vomiting induced by progressive myocardial disease is believed to be analogous to that caused by digitalis, which has been shown to be due to a reflex arising in the heart itself.

3. When coronary thrombosis occurs in a patient with preexisting narrowing of the smaller coronary arterial branches, a vicious cycle may ensue; the decline in cardiac output and small pulse pressure lead to further coronary insufficiency and progressive myocardial fibrosis which bring about a further decrease in cardiac output and perpetuation of the cycle.

4. In cases of heart failure in which there is a small pulse pressure with a high diastolic pressure, the outlook is poor because of the factors outlined.

The Measurement of the Lung-to-Face Time by Amyl Nitrite

Gross (*Am. Heart J.*, **30**:19, 1945) gives in the following lines the summary of his observations:—

1. A new method for the measurement of the lung-to-face circulation time, using amyl nitrite as an agent, is outlined. The technique of administration is described, and normal values and their correlations are established. The method is simple, needs no apparatus nor assistants, and can be performed by the examiner alone.

2. The amyl nitrite circulation time (a.c.t.) measures the functional capacity of the left ventricle and is determined essentially by the condition of the pulmonary circulation recognizable by the vital capacity. There exists a tendency of parallelism as much in the absolute value of both factors as especially in their modifications in different conditions of compensation in the same person.

3. The inverse correlation is established between the a.c.t. and the intensity of the warm sensation: more intense heat with shortened circulation time and *vice versa*.

4. In conditions of heart failure, the a.c.t. is prolonged, and the intensity of the warm sensation is diminished, but there is no strict parallelism with the clinical features.

5. In hyperthyroidism the a.c.t. is shortened and the intensity of the warm sensation is strongly reinforced. Emphysema or bronchial asthma, not complicated by heart failure, are characterized by normal a.c.t. and normal intensity of the warm sensation.

6. Subminimal a.c.t., except for existing intracardial or arteriovenous short circuits, never is observed with cardiac failure; largely prolonged a.c.t. never is observed without heart failure. Medium values of a.c.t. are as compatible in persons of normal circulation as in those with slight failures of it.

7. A differentiation between left or right ventricular failure is not possible, based upon the amyl nitrite measurement.

The test is done as follows:

The measurements were made on recumbent patients, after a rest period of ten minutes in a nonbasal condition. The amyl nitrite used in this study was obtained from ampoules which contain 4 minims of the drug and are covered by absorbent material. The time between the commencement of deep inspiration of the vapor of amyl nitrite and the appearance of a well-marked heat sensation in the face was registered by a centesimal chronometer, and represents the lung-to-face time as an expression of the trajectory from the pulmonary capillaries to the capillary bed of the face. Knowledge of certain peculiarities of the physiologic effects of breathing amyl nitrite vapors and adequate preparation of the patient for correct measurement are very important. Information must be given to lessen the possibility of nervous excitement before and during the process, in order to prevent changes in respiration and circulation which may cause significant errors in the measurement. The inhalation must be made through the nose, with the mouth kept closed. In this way the mixture of air with the amyl nitrite vapour is less than it would be if the vapour were inhaled through the mouth. Consequently, before taking the measurement, it is necessary to make several tests of the patient's respiratory behavior. This is done by placing the unopened ampoule directly under his nose and inviting him to take a deep and rapid breath, and then continue to breathe normally and quietly. Only after having made several trials, and being sure of the perfect collaboration of the patient, can the measurement be started. Attention must be drawn to the fact that the ampoule explodes when opened. By this warning the perturbing effect can be lessened or avoided. Before the process is begun, the patient is informed that, several seconds after the first and only deep

inhalation of amyl nitrite vapor, a definite sensation of heat will be felt in the face, together with a pounding of the pulses in the head and a certain feeling of heaviness and quickening of the heartbeat; these effects of the drug have no annoying intensity and will disappear within a few minutes. The patient is instructed to report immediately the first clearly felt sensation of heat in the fact by uttering the word 'Ya.' That represents the end of the process. The measurement by chronometer begins with the first and only deep breath and ends with the first clearly felt heat in the face, indicated by the patient's saying 'Ya.' The chronometer is then stopped. It is not feasible to substitute observation of flushing of the face by the examiner for the subjective sensation of heat felt by the person under examination, because nervous excitement and emotion, by the psychovasomotor reflex mechanism, are able to produce similar flushes before the inhalation of the amyl nitrite, but with no definite feeling of heat. The other effects of inhalation of amyl nitrite vapor, such as cough, pounding of the pulse, and tears, are inconstant and not suitable for making the end point of any measurement.

As a final observation about the technicalities of the measurement of the amyl nitrite circulation time (a.c.t.), the necessity of the patient's being recumbent during the test must be emphasized, in order to avoid incidents which may follow dizziness (faintness, even syncope.).

Hodgkin's Disease

Goldman and Victor (*New York State J. Med.*, **45**:1333, 1945) report 319 cases of Hodgkin's disease. The youngest patient in the group was 5 and the oldest 76 years of age. A clinical diagnosis of Hodgkin's disease can frequently be made by palpation of the involved lymph nodes. It is possible to count from 3 to 5 nodes in each of the involved group. The nodes may vary in size from 2 to 12 cm. As a rule more than one area is involved. Thirteen of the authors' patients showed involvement of the sternal nodes, never before mentioned in the literature. The skin was involved in 39 per cent of the patients. Roentgenographic findings in the chest characteristic only of this disease were never found. There was a gradual transition from a bilateral thickening of the hilar areas to a widening of the mediastinum and invasion of adjacent lung fields. Hodgkin's disease of the gastrointestinal tract was observed in only 2 patients. It was unusual to palpate the spleen in ambulatory patients. The abdominal form of Hodgkin's disease was observed in 27 patients. They exhibited weakness, loss of weight, intermittent bouts of fever and a more rapid course. Collapse of a vertebra may occur without symptoms of spinal cord compression. The characteristic changes in the sternal marrow were a polymorphonuclear shift to the right with severe toxic granulation, increased eosinophilia of young myeloid elements and increase in the monocytic series. Pregnancy occurred in 11 patients; therapeutic abortions were performed in 3, miscarriage resulted in 1, and the pregnancies were carried to term in the remaining 7. There was no evidence of Hodgkin's disease in the offspring. Even under the most optimal conditions permanent arrest of the disease has not been obtained, but useful life has been prolonged for many years. The patient should receive the smallest quantity of irradiation that is compatible with relative well-being just sufficient to cause gross disappearance of involved lymph nodes. The authors utilized a voltage of 200 kilovolts, a filtration of 0·5 copper and 1 aluminum, a port of 10 by 15 cm. and a skin-target distance of from 40 to 50 cm. Voltages that were either higher or lower produced inferior results. In addition to the irradiation the patient should receive supportive hermatinic therapy.

Infectious Mononucleosis

Press and others (*Ann. Int. Med.*, **22**:546, 1945) report 96 consecutive sporadic cases of infectious mononucleosis observed at the Jewish Hospital of Broklyn over a ten year period. Infectious mononucleosis is an acute benign infection of unknown etiology characterized by irregular fever, swelling of the lymph nodes, sore throat, splenomegaly and lymphocytosis with the presence of abnormal lymphocytes in the peripheral blood stream; the blood serum may contain antibodies against sheep erythrocytes in high titers. The disease has been described also under terms such as acute lymphadenosis with lymphocytosis, monocytic angina, lymphocytic angina, lymphatic reaction and glandular fever. Diagnosis of infectious mononucleosis is in order in the presence of a suspected clinical picture when the hæmatologic findings are positive. The blood smear has been the most constant and characteristic single laboratory feature in the recognition of this disease. A positive Paul-Bunnell test is strongly confirmatory, but its absence does not preclude the diagnosis. It is sometimes necessary to repeat this test before a positive reaction develops. Because of extreme diversity of manifestations of infectious mononucleosis the diagnosis may go unrecognized unless the disease is borne in mind and appropriate laboratory procedures are carried out.

Migraine Headache

Torda and Wolf (*Arch. Neurol. & Psychiat*, **53**:329, 1945, Ref. *J.A.M.A.*, **128**:1252, 1945) state that distention of cranial arteries induces pain of an aching quality. The speed with which vasoconstrictor agents such as ergotamine tartrate reduce the intensity of the headache aproximates the rate of constriction of the cranial arteries. In many patients the headache arises in the distended branches of the external carotid arteries, although any or all of the cranial arteries may be involved in migraine headache. Secondary to pain from prolonged distention of cranial arteries, the skeletal muscles of the neck and scalp contract and become painful. After several hours of such a headache the vessel may appear more prominent and distended. Instead of being collapsible it becomes rigid pipelike and less readily compressible. Patients may report that after the first hour or two of an attack of migraine the quality of the headache may change in that the initial pulsating or throbbing headache turns into a steady ache. To account for these changes the authors have postulated that after sustained dilatation there occurs thickening or œdema of the muscular and adventitial structures. Sections taken from the temporal artery of patients during attacks of migraine involving this structure revealed on microscopic examination that there was thickening of the arterial wall. Since comparable control sections during periods of freedom from headache cannot be obtained, the authors studied the structure of the arteries of the ears of 6 cats after infusion for two hours of 10 c.c. of mammalian isotonic solution of three chlorides containing 0·5 mg. of acetocholine bromide per hundred cubic centimeters. Measurements demonstrated thickening of the walls of the infused vessels. Ergotamine tartrate was less effective in constricting arteries with thickened walls than arteries with normal walls. It is suggested that during attacks of migraine the cranial arteries involved may undergo similar changes after prolonged vasodilatation. Such changes may explain the rigid, pipelike texture of arteries, the steady aching pain and the tenderness of these structures when

headache has persisted for many hours. Also these changes may explain the decreased ability of ergotamine tartrate to reduce promptly the intensity of prolonged headache.

Cure of Typhoid Carriers

Freemaster and Smith (*Am. J. Pub. Health*, **35**:368, 1945) say that as various chemical and biologic agents have been tried and found to be failures it has been necessary to return repeatedly to cholecystectomy as the only method which regularly cures an appreciable number of carriers. The authors review observations on 68 typhoid carriers operated on in Massachusetts between 1924 and 1944. There have been 63 cures and 5 failures. Medical treatment, even with sulphonamide compounds, cannot be relied on to eliminate the gallbladder focus. The authors have had 4 failure with sulphaguanidine and succinyl-sulphathiazole. To establish that a person is a bile carrier and supposedly a gallbladder carrier, it is necessary to demonstrate typhoid bacilli in the bile by duodenal drainage prior to operation or by culture taken from the gallbladder at the time of operation. The criteria of cure should consist of a careful bacteriologic follow-up for not less than twelve months of negative stool cultures and at least one negative bile. Cholecystectomy is still the only effective method of curing typhoid carriers.

Penicillin in Bacterial Endocarditis

Meads and others (*New England J. Med.*, **232**:463, 1945) present observations on 9 cases of subacute bacterial endocarditis caused by Streptococcus viridans and on 7 proved or probable cases of acute bacterial endocarditis due to other organisms, all of which were treated with sodium penicillin at the Boston City Hospital during 1944. In the 9 subacute cases the dose generally used was 25,000 units intramuscularly every two hours for two weeks. Seven of the patients are alive and have been free from evidences of active infection for one to eleven months. Two patients had recurrence of infection, 1 after four months and the other after only one month. It is not certain whether or not these recurrences represent reactivation of the original infection or reinfection. An additional fatal case of Streptococcus viridans endocarditis was treated. Improvement occurred in another extremely severe case with a characteristic clinical course of subacute bacterial endocarditis with multiple emboli, with survival three months after treatment, but no bacteria could be grown from the blood before penicillin was started. In the fatal cases heart failure resulted from extensive damage to cardiac structures. In the 7 cases of acute bacterial endocarditis small doses were generally used because of the greater susceptibility of the organisms. Three of these patients are living and well. The diagnosis in all the fatal cases was confirmed at necropsy but in those who survived it is only highly probable. Heparin was used together with penicillin in 3 of the Streptococcus viridans cases and in 2 of those due to the pneumococcus. There appeared to be no benefit from this therapy to justify the additional effort and risk. Early and intensive treatment with penicillin maintained for an adequate period offers the best hope for recovery or arrest of infection in cases of subacute and acute bacterial endocarditis.

Impetigo Contagiosa Treated with Microcrystalline Sulphathiazole

Mackenna and others (*Lancet*, **2**:35, 1945) write that statistical analysis of the results obtained in 1118 uncomplicated cases of impetigo treated in three different ways suggests the following answers to the two questions which the investigation was designed to answer:

Treatment with 15% sulphathiazole administered in either form is significantly better than treatment with lotio cuprozincica, except for the risk of sensitisation in 2½% of cases. The length of stay in hospital under treatment with either form of sulphathiazole is appreciably shorter than with lotio cuprozincica.

As between the two forms of sulphathiazole, the advantage lies with the microcrystalline form, but this advantage, though probably significant, was out-weighed in 1944 by scarcity of supply.

Detection of Cancer of the Urinary System

Papanicolaou and Marshall (*Science*, **101**:519, 1945, Ref. *Lancet*, **2**:182, 1945) write that an exfoliation of characteristic cells takes place, in cancer of the urinary system which can be diagnosed, they say, by examination of the urinary sediment. Their technique is as follows: Forty c.cm. of fresh urine, preferably obtained by catheter, is shaken with 10 or 20 c.cm. of 90% alcohol. After centrifuging for 10 minutes at 20,000 r.p.m. the supernatant fluid is removed and the sediment is spread with a wire loop on slides which have been thinly coated with albumin. Before the films are quite dry the smears are fixed in a solution of equal parts of ether and 95% alcohol, after which they are stained in the same way as vaginal smears. (Papanicolaou, *Science*, **95**:438, 1942). If cancer of the kidney or ureter is suspected material obtained by ureteral catheterisation is desirable. The diagnosis of cancer by this method depends on the cytological characters of the cellular deposit. Up to the present 83 cases have been investigated by this method, and without any knowledge of the clinical findings, 27 were reported as showing evidence of cancer. In 24 of the latter (89%) the diagnosis was afterwards confirmed and in the remaining 3 the nature of the trouble remained obscure. It is notable that there were no false positives in the series—that is to say, the diagnosis of cancer when made by examination of the urinary sediment was reliable.

The simplicity of the method, its cheapness, and its lack of inconvenience to the patient are in favour of its extended use. The only impediment seems to be the difficulty of interpreting the cytological appearances, which is no easy matter for those who lack the vast experience which Papanicolaou has had of this kind of work. This impediment is not, however, insurmountable.

Frozen Human Skin Grafts

Strumia and Hodge (*Ann. Surg.*, **121**:860, 1945) transplanted 41 autogenous split thickness grafts, preserved in the frozen state from one to sixty-one days, at temperatures of minus 20 to minus 25 C. (minus 4 to minus 13 F.) to 3 patients. These grafts resulted in 80·5 per cent permanent takes. Thirty-four control grafts of fresh skin in the same patients resulted in 86·4 per cent takes. The result of grafting does not appear to be affected by the time of storage of the grafts in the frozen state, at least within the experimental limits mentioned. Aside from the possible development of skin banks for homografts, the preservation of split thickness autogenous grafts in the frozen state allows the operator to obtain at one operation large numbers of grafts which may be employed for transplantation at any time later on.

Penicillin in Vincent's Angina

Schwartz (*J.A.M.A.*, **128**:704, 1945) writes that penicillin has been found to be of definite value in the treatment of Vincent's angina in 14 cases.

The recommended dose is 100,000 units administered intramuscularly in 20,000 unit doses every three hours. In mild cases smaller doses may be required and in unusually severe cases larger doses may be required.

Penicillin and Sulphonamides in Actinomycosis

Dobson and Cutting (*J.A.M.A.*, **128**:856, 1945) write that sixteen cases of actinomycosis were treated with sulphonamides or penicillin. These cases include 3 pulmonary, 2 abdominal and 11 of the cervicofacial types. Of the 16 cases treated, 7 may be considered cured and 7 arrested, while 2 ended fatally. *In vitro* tests corroborate the clinical impression of varying susceptibility of actinomyces to sulphadiazine and penicillin and of the slightly greater efficacy of sulphadiazine in certain instances. The results in these cases indicate that both penicillin and the sulphonamides are highly effective drugs in the treatment of actinomycosis.

Conservative Treatment of Human Bite Infections

Henry (*Military Surg.*, **97**:122, 1945) gives in the following lines a routine procedure in the treatment of all human bites:

1. All wounds should be immediately cleansed well with soap and water, followed by gentle debridement.
2. Culture all such wounds. (Dark field examinations and ten day anaerobic cultures are diagnostic aids.).
3. Tetanus antitoxin or booster shot for human bites, dog, cat, or horse bites.
4. Irrigate wound with hydrogen peroxide and Dakin's solution. If these are not available use warm saline.
5. Never suture or repair these wounds regardless of time interval. This is the most common serious error!
6. Leave wound wide open and sprinkle wound with sulpha crystals.
7. Hot $MgSO_4$ or boric soaks to extremity once daily for one week.

Check Wassermann-Kahn test on patient and repeat test in one month from time of bite.

9. Avoid amputation in presence of acute infection. Treat conservatively and allow nature to wall off process.
10. Check with x-ray for bone involvement at time of inquiry and again later for any complication because of the tendency of these cases to develop slowly into deep undermining wounds and with extension to bone.
11. Splint the extremity between treatments because rest to the part aids in the healing process.
12. Penicillin has very slight, if any effect on certain mixed infections. However a ten day treatment with penicillin would be indicated, using 100,000 units each day. Since penicillin is not a specific cure in mixed infections and in order to save any possible man hour loss, it is felt that penicillin should be used in addition to conservative surgical debridement, irrigation and adequate drainage of the anaerobic wound. Both reported patients in this paper, however, only received sulpha crystals locally in wound, but no sulpha or penicillin treatment orally or parenterally.
13. All human bite injuries should be well written up in the health record, treated conservatively, and observed carefully for complication. Emphasis should be placed on adequate drainage and an attempt to produce a state of aerobiasis in wound.

Laboratory Diagnosis

Dible (*Lancet*, **2**:305, 1945) at the summer meeting of the Association of Clinical Pathologists held in London on July 20 and 21, spoke on the *pathology of infective hepatitis* with special reference to hepatic biopsy. After demonstrating the method of liver puncture by the transpleural route with suction of a small piece of liver substance into the cannula by means of an attached syringe, and describing the alcohol-free fixation to preserve glycogen, and the staining used, he produced a series of slides illustrating the histological appearances in infective hepatitis. The essential features were rarefaction at the centre of the lobule with derangement of columns of cells, the apearance of bizarre forms with swollen cells associated with a cellular infiltration of bile-ducts, and generally a reduction in the width of the lobule. There was, however, good retention of the reticulin arrangement of the liver lobule. Dr. Dible demonstrated varying degrees of these changes in various forms of jaundice, including infective jaundice, serum jaundice, and neoarsphenamine jaundice, and suggested that the icterogenic agent was similar and that the toxic pathological changes seen after biopsy were also similar.

Major C. E. Van Rooyen described the *rapid diagnosis of smallpox* by demonstration of elementary bodies from the vesicles. From his experience of several hundred cases in the Middle East he maintained that this was a simple matter and their recognition to a trained observer was reliable. The findings had been proved correct in several cases in which they were doubted because at first the clinical appearances were atypical. A second paper dealt with rickettsial agglutination tests in typhus.

Prof. A. D. Gardner read a paper on the *laboratory diagnosis of Weil's disease*. He had investigated material from 900 suspected cases and had found 150 positive. From his records it was clear that jaundice was not always present and that the non-icteric cases probably had a better prognosis. Case-mortality in the series differed with age; in old people it was 50% but in young people only 5%, the overall mortality being 12%. The agglutination tests had been carried out with formolised suspensions of the leptospira which had been grown in 12% rabbit serum in glass-distilled water. These suspensions had remained stable in his hands for years. Dr. Gardner expressed the hope that now that penicillin shows such great promise in the treatment of the disease, attempts at diagnosis will be made earlier in the disease without waiting for jaundice, which sometimes occurred in this series as late as the 8th or 9th day, although it was commonest on the 5th.

Squadron-Leader E. M. Darmady's paper on the *traumatic uraemia syndrome* produced an excellent discussion in which various contributors showed how the syndrome was produced by many factors, including trauma, crush, and severe transfusion reactions, all of which gave similar histological appearances in the kidneys. In this discussion Dr. Joan Ross described cases of anuria she had collected from the battle areas.

Dr. G. R. Osborn dealt with the *action of thiouracil on goitres* and showed a series of sections demonstrating the main changes. Macroscopically the tumour was often hard, pure white, with no appearance of colloid—very suggestive in appearance of carcinoma. Even microscopically the changes frequently included large cells with hyperchromatic nuclei which also might be mistaken for a carcinoma. Dr. Osborn agreed that thiouracil was now the best preoperative means of treatment in the diffuse toxic goitre.

Dr. W. H. Grace described a long series of cases of sudden death in infancy, and explained the difficulties with which even an experienced forensic pathologist might be faced when presented with a 'dead infant.' Asked whether he believed in status lymphaticus he answered that he regarded this as the fifth ace, to be kept up the sleeve for special emergencies.

Papers were also read by Dr. M.O. Skelton, who demonstrated fatal *tracheo-bronchial diphtheria* in an infant of five weeks. Dr. R. A. O. Williams spoke on the value of preliminary fluid culture for the *isolation of pyogenic cocci* when a larger yield is desired. Dr. A. F. Sladden spoke on the *routine examination for diphtheria*, using a tellurite-Loeffler medium which he claimed as a simple and effective substitute for the elaborate media now in use. Dr. K. B. Rogers described a method of suspending *sedimentation tubes* in a jar of water at a controlled temperature because of the discrepancies which occurred as a result of temperature variations in this test. A discussion was opened by Dr. E. N. Davey followed by Dr. S. C. Dyke on the *investigation of the allergic state*. Some doubt was thrown by some speakers on the value of skin tests in demonstrating sensitivity, but generally it was held that they are of great value in indicating particularly single-allergen sensitivity.

The meeting ended with a paper by Dr. H. N. Stafford on *the corpse, the pathologist, and the coroner*. Expounding the duties and limitations of the pathologist in regard to the coroner, he gave his interpretation of the 1887 Coroners Act with the amending act of 1926. He made it clear that a pathologist may make a post-mortem examination if he considers, or is told, that the death is due to natural causes, and that in any case no 'assault' can be committed on a corpse by so doing. The overriding consideration was that there should be cooperation between the medical men and the coroner, and the coroner must certainly not be obstructed in his duties.

Diphtheritic Myocarditis

Ball (*Am. Heart J.*, **28**:704, 1945) in reporting two cases of diphtheritic myocarditis in adults writes that the electrocardiographic changes observed in the two cases described would indicate that there was severe and extensive myocardial involvement. At no time did these patients have any complaints referable to the cardiovascular system and, at no time, were there any clinical findings to suggest involvement of the heart. In both cases, the changes were reversible and shifting from day to day, suggesting that the changes observed are "toxic" in origin and not due to any structural damage to the heart muscle: In conclusion the author writes that the electrocardiographic changes conform to a type that is easily differentiated from those observed in myocardial infarction due to coronary artery occlusion. The S-T interval is always depressed in diphtheritic myocarditis. The changes are reversible and 'Shifting.' These effects are probably toxic in origin in diphtheritic myocarditis. There was no clinical evidence of heart disease in either case described.

XXII ALL-INDIA MEDICAL CONFERENCE, AMRITSAR

PROGRAMME

22nd December, 1945

3	p.m.	to 4	p.m.	Working Committee Meeting
4	p.m.	to 4-30	p.m.	Tea
4-30	p.m.	to 6	p.m.	Amalgamation Committee
6	p.m.	to 8-30	p.m.	Working Committee Meeting
8-30	p.m.	to 9-30	p.m.	Dinner
9-30	p.m.	to onward.		Working Committee Meeting

23rd December, 1945

Morning—				Working Committee Meeting to be continued if necessary.
After Lunch—				
2	p.m.	to 4	p.m.	Central Council Meeting
4	p.m.	to 4-30	p.m.	Tea
4-30	p.m.	to 8-30	p.m.	Central Council Meeting
8-30	p.m.	to 9-30	p.m.	Dinner
9-30	p.m.	onward.		Central Council Meeting

24th December, 1945

Morning—				Central Council Meeting to be continued if necessary after breakfast (8-30 a.m. to 9 a.m.) upto 10-30 a.m.
11	a.m.	to 11-20	a.m.	Inauguration of the Conference
11-20	a.m.	to 11-50	a.m.	Address of the Chairman of the Reception Committee
11-50	a.m.	to 12-50	p.m.	Presidential Address
1-15	p.m.	to 2-15	p.m.	Lunch
2-30	p.m.	to 3-15	p.m.	Election of the Subjects Committee
3-15	p.m.	to 3-30	p.m.	Opening of the Exhibition
3-30	p.m.	to 4-30	p.m.	Visit to the Exhibition
4-30	p.m.	to 5-30	p.m.	At home
5-30	p.m.	to 8-30	p.m.	Scientific Session (Surgery)
8-30	p.m.			Dinner

25th December, 1945

8-30	a.m.	to 9-30	a.m.	Breakfast
9-30	a.m.	to 1	p.m.	Subjects Committee Meeting
9-30	a.m.	to 11	a.m.	Scientific Meeting (Tuberculosis)
11	a.m.	to 12-30	p.m.	Pathology
1	p.m.	to 2	p.m.	Lunch
2	p.m.	to 4	p.m.	Open Session of the Conference
4-30	p.m.	to 6-30	p.m.	At Home and Visits to Mills
6-30	p.m.	to 8-30	p.m.	Scientific Session (Medicine)
8-30	p.m.	to 9-30	p.m.	Dinner
9-30	p.m.			Subjects Committee Meeting

26th December, 1945

8-30	a.m.	to 9-30	a.m.	Breakfast
9-30	a.m.	to 12-30	p.m.	Scientific Session (Medicine)
12-30	p.m.	to 1	p.m.	Visit to Exhibition
1	p.m.	to 2	p.m.	Lunch
2	p.m.	to 4	p.m.	Open Session
4	p.m.	to 8-30	p.m.	At Home and Visits to Mills
8-30	p.m.			Dinner
9-30	p.m.	onward.		Subjects Committee Meeting

27th December, 1945

8-30	a.m.	to 9-30	a.m.	Breakfast
9-30	a.m.	to 11	a.m.	Scientific Session (Eye)
9-30	a.m.	to 11	a.m.	Gynaecology
11	a.m.	to 12-30	p.m.	Radiology
11	a.m.	to 12-30	p.m.	Nose and Throat
12-30	p.m.	to 1	p.m.	Visit to Exhibition
1	p.m.	to 2	p.m.	Lunch
2	p.m.	to 4	p.m.	Open Session
6-30	p.m.	to 8	p.m.	Scientific Session
8	p.m.			Dinner

NOTES & NEWS

THE TEACHING AND PRACTICE OF CHEMICAL PATHOLOGY

Because of the present unsatisfactory position of chemical pathology, a committee of the chemical pathologists of the London teaching hospitals has prepared a memorandum on the subject. The members agree with the recommendation in the Goodenough report that chemical pathology should form a separate department and go under the direction of a professor, reader or senior lecturer. To this they would add that the chemical pathologist should be a full member of the medical committee of his hospital. Undergraduate teaching in chemical pathology should be given in the form of a short introductory course at the beginning of the clinical period, with other lectures over the remaining clinical years. The committee differs from the Goodenough proposal which allots routine chemical work to the clinical pathologist, because the chemical pathologist would be largely cut off from the principal source of his inspiration, and his teaching of the basic principles and routine methods would tend to lose contact with current practice. If, for example, no routine blood urea estimations were performed in his department, both the technic and the interpretation of this test would eventually become remote from his personal experience. The standard of chemical work would become lower and a retrograde step would be taken against the tendency to specialization in pathology, which is inevitable. In a hospital of 1,000 beds the routine work in haematology and bacteriology will be so much that the addition of routine chemical tests would be an excessive burden. A closer liaison between the preclinical biochemical and the chemical pathology departments in the medical schools is advised.

The following curriculum, based on a total of twenty-four hours' instruction during the clinical period, is recommended in the report: 1. An introductory course of six hourly periods in the first clinical year, dealing with general principles and including instruction on collection of specimens and urine testing. 2. A general course of eighteen hourly periods during the second and third clinical years, covering the whole subject of the application of chemical methods to clinical problems. 3. A limited number of lectures on special aspects and recent advances during the preregistration year.—*J.A.M.A.*

THE MOSCOW MEDICAL INSTITUTE

Tsarist Russia's thirteen faculties of medicine and 1,800 students have been increased under the Soviet rule to seventy-two medical institutes with a student body of 115,000. Russia's 20,000 doctors in 1913 have now grown to 130,000. Still the number of doctors is not adequate to meet the nation's needs and to staff its expanding network of medical institutes. These graduate as many as 20,000 doctors a year. Following is a description of the type of work performed by one of these schools. The Moscow Medical Institute, of which Andrei Likhachev is director, is celebrating its 180th anniversary this year. A number of Russian scientists who have added brilliant pages to medical history received their training here. Among these may be mentioned the surgeon Nikolai Pirogov and the internist Sergei Botkin. Ivan Sechenov, author of "Brain Reflexes," was one of its teachers. The institute has made valuable contributions in every field of theoretical and practical medicine. The student body today numbers 4,000. The first two years are devoted to the study of anatomy, physiology, histology, biology and biologic chemistry. Beginning with the third year, students are introduced to clinical work. After receiving their general training they specialize in hospitals and clinics in accordance with their inclinations and abilities.

On the teaching staff are men of the type of Nikolai Burdenko, chief surgeon of the Red army; the pathologist Alexey Abrikosov, who has trained an army of pathologists in the course of his thirty-five years' work at the institute, and Boris Zbarsky, who emblamed the body of Lenin and is now teaching biochemistry. All these men have had the highest civilian award, Hero of Socialist Labour, conferred on them. The staff numbers 70 professors, 100 docents and over 250 instructors. Eleven are members of the Medical Academy of Sciences.

The course of study was increased this year from five to six years. There are no tuition fees; 95 per cent of the students receive government stipends. Sixteen of the best students receive the Stalin scholarship. Over 30 per cent live in institute dormitories. In addition to their regular studies students may attend thirty circles of study in various specialized scientific fields. Five hundred students working in these circles are given opportunity to engage in independent research work.

Very popular is the "Free Day" club, which is conducted by the students and teachers and which arranges concerts, lectures by poets and novelists, and debates.

Students who attain a high average and display ability for research and teaching are given an opportunity to continue their work at the institute in a three year postgraduate course, during which they work in laboratories and clinics under the guidance of professors and write their theses for the degree of candidate of science. Throughout their postgraduate period students receive government stipends large enough to enable them to devote themselves entirely to their work.

The institute has trained 34,000 doctors in its one hundred and eighty years of existence. During the war, Academician Burdenko set up an experimental station in the institute to test new drugs and methods of treatment of wounds and of chemical and thermal burns.

The Chair of Food Hygiene developed recipes for so-called supplements, which increase the assimilability and nutritive value of various food concentrates. The Chair of Communal Hygiene has developed methods of simplifying chlorination of the water supply for army field units.

The institute graduated 3,300 doctors during the war. In their leisure time students work with enthusiasm in hospitals and take an active part in hygienic inspection of the cities. Many of the students have won government medals and orders. The institute was awarded the Order of Lenin in 1940, on the occasion of its 175th anniversary, in recognition of the services its teaching staff has rendered in training medical men and in advancing medical science.—*J.A.M.A.*

PROPOSED FORMATION OF A GROUP OF DERMATOLOGISTS WITHIN THE BRITISH MEDICAL ASSOCIATION

A number of members of the British Medical Association who are dermatologists have petitioned the association for the formation within it of a group of dermatologists. They are engaged in a specialized branch of which the importance is becoming increasingly recognized, but the number in one division of the association is too small to put forward the medico-political problems of the speciality adequately. They therefore hold that the formation of a group of those whose work is exclusively dermatologic would be an advantage both to the group and to the association.—*J.A.M.A.*

GRANT FROM CHEMICAL FIRM FOR SCIENTIFIC RESEARCH IN INDIA

Lord McGowan, president of Imperial Chemical Industries, has written to Professor Wadia, president of the National Institute of Sciences of India, offering a number of research fellowships for the encouragement of Indians in chemistry, physics and biology, to be held at Indian Universities and institutions. The sum offered is $100,000 over the next five to seven years. In his letter Lord McGowan states that untill recent years the Royal Society was hampered by lack of funds and provision for the maintenance of scientific workers. This difficulty was overcome by the generosity of various benefactors including industrialists such as Mond and Messel. There seemed no better way of encouraging the advance of science in India and with it the general prosperity of the country than by offering these fellowships. Each will be worth $110 a month and will be tenable in the first instance for two years with possibility of extension up to three years. In addition there will be a grant for research expenses. The fellowships will be open to persons irrespective of sex, race or religion who are under the age of 35 years.—*J.A.M.A.*

ROCKEFELLER TRAVELLING FELLOWSHIPS TO BE RESUMED

It is announced by the Medical Research Council the preliminary arrangements have been made for the resumption of the Rockefeller Medical Fellowships. These are provided from a fund entrusted to the Council by the Rockefeller Foundation of New ork. The fellowships are intended of graduates resident in Britain who have had some training in research work in clinical medicine or surgery or some other branch of medical science and who are likely to profit by a period of work at a centre in the United States or elsewhere abroad before taking up positions for higher teaching or research in Britain. It is hoped to make a limited number of awards during the academic year 1945-1946, depending on the availability of candidates and the facilities for travel.—*J.A.M.A.*

FELLOWSHIPS TO PROMOTE THE STUDY OF THE MAINTENANCE OF HEALTH

The Nuffield Foundation announces yet another benefaction. It proposes to award a number of medical fellowships to help promising men and women who wish to follow an academic career in social medicine, child health, industrial health and psychiatry to obtain at home or abroad the necessary post-graduate training and experience. More men and women trained in research and teaching are needed to secure the continued advance of medical knowledge and the standard of medical education. The foundation believes that there is a special need for carefully selected persons to have opportunities for studies which relate to the promotion and maintenance of health as distinct from the recognition and treatment of established disease. It hopes that the fellowships being offered will help to meet this need.

Normally the annual value of a fellowship will be between $2,500 and $4000. It may be awarded for one or more years but as a rule for not longer than three years. Candidates must hold a university degree in medicine registrable in Britain and have had general clinical experience since qualification. In order that doctors serving overseas may not be at a disadvantage, the trustees have refrained from requiring applications to be submitted by a specified date. Medical officers serving with the armed forces may apply now for fellowships tenable on demobilization.—*J.A.M.A.*

BICENTENARY OF THE ROTUNDA

Two hundred years is a long time in the history of any institution, and it is no small credit to the vision of the founder of the Rotunda Lying-in-Hospital, Dublin, that the original buildings, largely unchanged, are still in use for their original purpose.

Bartholomew Mosse, the founder and first master, was born in 1712, son of the rector of Maryborough. After a medical education in Dublin, and a short period as an army surgeon in Minorca, he studied midwifery in England, Holland, and France, and on his return to Dublin in 1742 was admitted a licentiate in midwifery of the King's and Queen's College of Physicians in Ireland. From that date 'he quit the practice of surgery' and became a man-midwife. Three years later, on March 15, 1745, he opened the first lying-in hospital in the Three Kingdoms. It contained a few beds for the reception of patients, and despite great difficulty in raising funds, and the active opposition of Mosse's medical brethren, it grew and flourished; by July, 1746 204 women had been delivered of 208 babies, with 1 maternal and 7 foetal deaths no bad record for the time.

Encouraged by the success of his small beginning, Mosse planned a larger and more ambitious scheme, and on July 9, 1751, was laid the foundation-stone of the present Rotunda building, the famous Georgian architect, Richard Castle, being responsible for the plans and design. The building was completed and opened for patients on Dec. 8, 1757, the intervening six years being for Mosse a nightmare of debt and difficulties. Accused by his colleagues of self-aggrandisement, harassed by his creditors, and actually arrested for debt, he still worked on at the old hospital and continued to build the new. The royal charter of 1756 is the instrument by which the hospital is still governed.

In 1759, when only 47, Mosse died, having been for 14 years the originator and inspirer of the care of lying-in women in these islands. Since that date the Rotunda has grown and developed—by additions, rather than by alterations—and now it celebrates its 200th year.—*Lancet.*

SAFETY OF ICE-CREAM

To the public health worker ice-cream has much in common with milk. It is eaten mainly by children, it is a rich bacteriological medium, and it is known to have carried many of the same diseases as milk. In this country the dangers of contaminated ice-cream have been given small consideration and it is only when conditions of manufacture are grossly insanitary that the Food and Drugs Act, 1938, is called on to protect the public. The misconception that freezing destroys all bacteria persists, even among those who should know better. In America ice-cream made from unpasteurised milk has been found to contain as many as 37 million organisms per c.cm. about the same number as sewage. Diseases which may be spread by ice-cream include the enteric group, dysentery, and scarlet fever, and recent reports in the daily press suggest that staphylococcal food-poisoning must be added to the list. With these and other points in mind, there appears to be a case for tightening up legislation on the methods of manufacture and dispensing of ice-cream. A new order issued by the Ministry of Food should help to prevent the danger to which consumers of ice-cream may be exposed if the dried egg used in its manufacture is infected. What the chances of such infection are has not yet been reported, but some samples of dried egg do contain salmonella organisms. The order prohibits the use without a licence of dried egg in the manufacture of synthetic cream, ice-cream, and baker's

(Continued at foot of page 66, col. 1)

CORRESPONDENCE

The Editor is not responsible for any views expressed by contributors.

VITAMIN A IN TUBERCULOSIS

Sir,—In view of the fact that calcium and cod-liver oil are being extensively used without any immediate effect, may it not be possible that the effect of the oil is due to its vitamin A content. It would be quite in keeping with the fact that its precursor, carotene, which is abundantly available in fresh vegetables during the change of air may be responsible for a quicker arrest of early cases. I believe, massive doses of vit. A in 200000 to 300000 I. U. given intramuscularly every 2nd or 3rd day may be more helpful than the routine use of calcium and others. I feel it controls the toxæmia (fever) more quickly with surprising promptness in some cases (pulmonary) in conjunction with absolute rest.

Bombay — P. H. KHAKHAR

(*Continued from page 65*)

cream filling. Under this licence manufacturers must pasteurise a mix which contains dried egg; not more than two hours must elapse between reconstituting and pasteurising the dried egg; and the treated product must not be exposed to a temperature at which pathogens can multiply. These provisions are reasonable but until the authorities in this country release more information about the bacteriology of dried egg many will fail to see the reason for them. Efficient pasteurisation of a substance like dried egg is not easy and it will be difficult to know if the order is being properly carried out. The new regulations are aimed at new dangers; they still do not ensure that the freshly painted barrods will contain wholesome or safe food.—*Lancet.*

THE TEACHING OF PEDIATRICS

A pediatric committee of the Royal College of Physicians has presented an important report on the teaching of pediatrics. It suggests that the student's attention should be directed to the growth and development of children while he is still learning biology, physiology and anatomy and that the diseases peculiar to childhood should find a place in his studies of pathology and psychology. In his midwifery course he should be taught by a pediatrician about health and disease in the newborn. He should also spend eight sessions at a child welfare centre, where he will be taught by a pediatrician or a suitably qualified maternity and child welfare officer. Courses in care of the newborn and in child welfare should precede his course in general clinical pediatrics, which should occupy not less than a third of his whole time given to clinical medicine and should include a resident period of a month. In the study of social medicine the social services dealing with children should be given proper weight, so that the student may gain some insight into the school medical service, child guidance centres and children's courts.

The Teaching Unit—The report holds that a hospital centre closely linked to a university and with a separate children's hospital attached to it, has much to recommend it. A university department of pediatrics, housed in a children's hospital, would forward teaching and research. Alternatively the university pediatric department might be developed as part of a general undergraduate teaching centre admitting 80 to 100 students a year. In any case it should have at least 100 beds for general medical and surgical cases and possibly additional beds for tonsillectomy. At least 20 more beds should be set aside for infectious diseases, and the department should be linked to an appropriate fever hospital. Students should also have access to rheumatic heart homes, orthopedic hospitals and institutions for tuberculous children, so that they can study disease in childhood, and they should see rehabilitation applied in convalescent homes. In London much larger children's units will have to be developed in many medical schools; meanwhile students should get the necessary experience in children's hospitals. In provincial schools the children's hospitals will provide the main teaching in pediatrics, though these should in due course become university centres. The staff of the children's department should consist of a whole time director of professional rank, a whole time senior assistant, a registrar and a resident house officer. Also there should be two part time pediatricians of the standing of physicians or assistant physicians. A senior-pathologist should take a special interest in the pathology of children's diseases, and similarly a senior radiologist in x-ray examinations.—*J.A.M.A.*

OBITUARY

DR. ALI AHMAD, L.M.S.

Dr. Ali Ahmad was born in the year 1877 A.D. in the village Çhak Kazi Nizam in the District if Muzaffarpur. He passed the Extrance Examination of the Calcutta University from a private High School of Muzaffarpur in the year 1896. He got admission in the Bihar National College and passed the B.A. Examination in 1898. He joined the Calcutta Medical College and passed the L.M.S. Examination in 1906. After qualifying, he joined the Bengal Medical Service as an Asst. Surgeon was posted to the 24 Perganas District in 1907.

He was deputed on Plague duty in 1908 at Bhagalpur and also worked in Famine Relief Duty in 1909 in Champaran. His work was highly appreciated and he got a certificate of merit. He then worked as a Supernumerary Asst. Surgeon in the Temple Medical School, Patna, in 1910 for 6 months. He was then transferred to Muzaffarpur as an Assistant Surgeon in 1910.

In a few months, he was called back to join as Asst. Surgeon in charge of the Patna City Hospital in 1910 and remained there till 1918. He was then transferred to Hazaribagn and then to Bhagalpur and then to Dumka from where he went on long leave for about 2 years and, in 1921, resigned the Asst. Surgeonship to start his career as a private medical practitioner in Patna City where he was the top-most practitioner till his death on the 22nd Oct. 1945. He died of cardiac dilation and bronchopneumonia. He leaves behind his 3 sons and 5 daughters and a widow.

He did not take much part in public activities but was a profound scholar of Urdu literature. He was a member of the Municipal Medical Committee for several years and also a member of the Mahomedan Educational Committee of Patna City. Since the last few years he was also a member of the University Examination Board.

He always took a keen interest in all matters affecting the dignity of the medical profession. He was a Foundation Member of the Patna Medical Association and later its Vice-President. He was the Chairman, Reception Committee of the 1st Bihar Provincial Medical Conference. About 2 years back, he was elected to be the President of the Patna Branch of the Indian Medical Association but could not accept it due to ill health. He was generally loved and respected for his independent outlook and broad views.